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Electrospray Mass Spectrometry of Chemical Warfare Agents, Degradation Products and Related Compounds

Paul A. D'Agostino, Claude L. Chenier and James R. Hancock
Defence Research Establishment Suffield

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Technical Report

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Authors

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Abstract

Over the past several years Defence Research Establishment Suffield (DRES) developed LC-ESI-MS methods for the analysis of a variety of samples of chemical defence interest. These samples included hydrolysed munitions grade mustard, degraded O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothiolate (VX), snow contaminated with sarin (GB), soil contaminated with sarin (GB) and soman (GD), munitions grade tabun (GA), failed synthetic products and synthetic standards. During these investigations DRES acquired ESI-MS data for sixty chemical warfare agents, degradation products and related compounds. Data were obtained with a resolution of 5000 (50% valley definition) in the continuum mode at several sampling cone voltages. At lower sampling cone voltages the mass spectra were dominated by protonated, sodiated and protonated acetonitrile adducts and/or their dimers that could be used to confirm the molecular mass of each compound. Structural information was obtained by inducing product ion formation in the ESI interface at higher sampling cone voltages. Representative data obtained at both lower and higher sampling cone voltages were selected for entry into the DRES ESI-MS Database as part of a collaboration between Canada (DRES) and The Netherlands (TNO Prins Maurits Laboratory).

Résumé

Durant ces dernières années, le Centre de recherches pour la défense, Suffield (CRDS) a mis au point des méthodes CL-ENI-SM (chromatographie liquide – ionisation par électronébulisation – spectrograhie de masse) pour analyser une variété d'échantillons d'intérêt pour la défense chimique. Ces échantillons comprenaient de l'ypérite à munitions hydrolysée, du méthylphosphonothiolate de O-éthyle et de S (diisopropylamino-2 éthyle) (VX) dégradé, de la neige contaminée par du sarin (GB), du sol contaminé par du sarin (GB) et du soman (Gd), du tabun à munitions (GA), des produits synthétiques incomplets et des normes synthétiques. Durant ces études, le CRDS a acquis des données SM-ENI pour soixante agents de guerre chimique, produits de dégradation et composés reliés. Les données ont été obtenues avec une résolution de 5000 (à un niveau équivalent à 50% du pic chromatographique) en mode continu des tensions des entonnoirs de prélèvement. À des tensions plus faibles, les spectres de masse étaient dominés par des adduits protonés, de sodium et acétonitriles protonés et/ou des dimères qui pourraient être utilisés pour confirmer la masse moléculaire de chaque composé. L'information structurelle a été obtenue en induisant la formation des ions du produit dans l'interface ENI à des tensions plus hautes des entonnoirs de prélèvement. Des données représentatives obtenues avec des tensions d'entonnoirs de prélèvement à la fois plus hautes et plus faibles ont été sélectionnées pour être entrées dans la base de données ENI-SM du CRDS durant les travaux de collaboration entre le Canada (CRDS) et les Pays-Bas (laboratoire Prins Maurits TNO).

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Executive summary

Introduction: The Canadian Forces (CF) and its allies may be called on to perform peacekeeping or battlefield operations in regions of the world where there is a significant threat of chemical/biological (CB) warfare agent use. To operate effectively in these theatres they must be able to identify the CB agent used. Mass spectrometry (MS) is a powerful analytical technique for the identification of both known and unknown compounds and DRES is currently investigating this instrumental technique in fulfillment of CF CB detection and identification requirements.

Results: Over the past several years DRES developed liquid chromatography-electrospray-mass spectrometry (LC-ESI-MS) methods for the analysis of a variety of contaminated samples. During the course of these investigations DRES acquired ESI-MS data for sixty chemical warfare agents, degradation products and related compounds. Representative data were selected for entry into the DRES ESI-MS Database as part of a collaboration between Canada (DRES) and The Netherlands (TNO Prins Maurits Laboratory).

Significance: The CF and its allies may be deployed in regions of the world where there is a significant threat of chemical/biological warfare agent use. Gas chromatography-mass spectrometry, while suitable for the direct analysis of organophosphorus chemical warfare agent in organic extracts, is usually not preferred for the direct analysis of aqueous samples or extracts since these samples normally require additional sample handling steps and derivatization prior to analysis. LC-ESI-MS is being used increasingly, as electrospray mass spectrometric data may be used to directly identify chemical warfare agents, degradation products and related compounds in collected aqueous samples or extracts. Identification of the CB agent is of importance since the results of such analyses would contribute to the development of strategic and political positions regarding future military operations and would facilitate the dissemination of technical advice to in-theatre field commanders and medical personnel.

Future Plans: The mass spectra reported in this database would be valuable for the identification of chemical warfare agents, degradation products and related compounds samples collected by the military or in support of Chemical Weapons Convention inspections. The database will be updated as part of the on-going collaboration between Canada and The Netherlands.

D'Agostino, P.A., Chenier, C.L., Hancock, J.R. 2002. Electrospray Mass Spectrometry of Chemical Warfare Agents, Degradation Products and Related Compounds. DRES TR 2002-028. Defence Research Establishment Suffield.

Sommaire

Introduction: Les Forces canadiennes (FC) et leurs alliés peuvent être appelés à exécuter des opérations de maintien de la paix et des opérations sur les champs de bataille dans les régions du monde où il existe une menace sérieuse d'utilisation d'agents chimiques et biologiques (CB). Pour opérer de manière efficace dans ces théâtres, les FC doivent être en mesure d'identifier les agents CB utilisés. La spectrométrie de masse (SM) est une technique analytique d'identification des composés à la fois connus et inconnus. Le Centre de recherches pour la défense, Suffield (CRDS) est en train d'étudier cette technique instrumentale dans le but de répondre aux exigences des FC de détection et d'identification CB.

Résultats : Ces dernières années, le CRDS a mis au point des méthodes CL-ENI-SM (chromatographie liquide – ionisation par électronébulisation – spectrograhie de masse) pour analyser une variété d'échantillons contaminés. Durant le cours des recherches, le CRDS a acquis des données SM-ENI pour soixante agents chimiques de guerre, produits de dégradation et composés reliés. Les données représentatives ont été sélectionnées pour être entrées dans la base de données SM -ENI du CRDS durant les travaux de collaboration entre le Canada (CRDS) et les Pays-Bas (laboratoire Prins Maurits TNO).

La portée des résultats : Les FC et leurs alliés peuvent être appelés à se déployer dans les régions du monde où il existe une menace sérieuse d'utilisation des agents de guerre chimique et biologique. La spectrométrie de masse de chromatographie des gaz convient pour l'analyse directe des agents de guerre chimique organophosphorés mais elle n'est cependant pas la meilleure méthode pour l'analyse directe des échantillons aqueux ou des extraits, étant donné que ces échantillons requièrent normalement des étapes de manipulation d'échantillons additionnelles et une dérivatisation antérieure à l'analyse. La méthode CL-ENI-SM est de plus en plus utilisée, les données SM-ENI pouvant être utilisées pour identifier les agents de guerre chimique, les produits de dégradation et les composés reliés directement à partir d'échantillons aqueux ou d'extraits. L'identification des agents CB est de grande importance puisque les résultats de telles analyses contribueront au développement des positions stratégiques et politiques des futures opérations militaires et faciliteront la dissémination des conseils techniques aux commandants sur le champ des théâtres d'opérations et au personnel médical.

Les buts futurs : Les spectres de masse introduits dans les bases de données seront précieux pour l'identification des agents de guerre chimique, les produits de dégradation et les échantillons composés reliés cueillis par le militaire ou en soutien aux inspections de la Convention sur les armes chimiques. Étant donné la collaboration continue entre le Canada et les Pays-Bas, la base de donnée continuera d'être mise à jour.

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Table of contents

Abstract i

Résumé i

Executive summary iii

Sommaire iv

Table of contents v

List of figures vi

List of tables viii

Introduction 1

Experimental 3

Results and Discussion 4

LC-ESI-MS separations 4

LC-ESI-MS sensitivity 7

ESI-MS mass spectral differences 7

Conclusions 72

References 73

List of figures

Figure 1. Diisopropylamine (101) 12

Figure 2. 2,2'- Thiodiethanol (Thiodiglycol) (122) 13

Figure 3. Ethyl methylphosphonic acid (124) 14

Figure 4. Isopropyl methylphosphonic acid (138) 15

Figure 5. Ethyl ethylphosphonic acid (138) 16

Figure 6. Isopropyl methylphosphonofluoridate (Sarin, GB) (140) 17

Figure 7. Diethyl methylphosphonate (152) 18

Figure 8. Isopropyl methyl methylphosphonate (152) 19

Figure 9. Ethyl dimethylphosphoramidic acid (153) 20

Figure 10. Tetramethyl phosphorodiamidic cyanide (161) 21

Figure 11. O-Ethyl N,N-dimethylphosphoroamidocyanidate (Tabun, GA) (162) 22

Figure 12. Cyclohexyl methylphosphonic acid (178) 23

Figure 13. Hexamethylphosphorotriamide (179) 24

Figure 14. Cyclohexyl methylphosphonofluoridate (GF) (180) 25

Figure 15. Pinacolyl methylphosphonic acid (180) 26

Figure 16. Diisopropyl methylphosphonate (180) 27

Figure 17. Ethyl tetramethylphosphorodiamidate (180) 28

Figure 18. Diethyl dimethylphosphoramidate (181) 29

Figure 19. 3,6-Dithia-1,8-octanediol (182) 30

Figure 20. Triethyl phosphate (182) 31

Figure 21. Pinacolyl methylphosphonofluoridate (Soman, GD) (182) 32

Figure 22. 8-Chloro-6-oxa-3-thia-1-octanol (184) 33

Figure 23. Diisopropyl phosphorofluoridate (DFP) (184) 34

Figure 24. Tributylamine (185) 35
Figure 25. 2-(Diisopropylamino)ethyl ethyl sulfide (189) 36
Figure 26. Diisopropyl ethylphosphonate (194) 37
Figure 27. Ethyl isopropyl dimethylphosphoramidate (195) 38
Figure 28. Diethyl isopropyl phosphate (196) 39
Figure 29. Pentyl dibutylamine (199) 40
Figure 30. 2,2',2''-Trichlorotriethylamine (HN3) (203) 41
Figure 31. 1,7-Dioxa-4,10-dithiacyclodecane (208) 42
Figure 32. Diisopropyl dimethylphosphoramidate (209) 43
Figure 33. Diisopropyl ethyl phosphate (210) 44
Figure 34. Diisopropyl chloromethylphosphonate (214) 45
Figure 35. Triisopropyl phosphate (224) 46
Figure 36. N,N'-Dicyclohexylurea (224) 47
Figure 37. 6-Oxa-3,9-dithia-1,11-undecanediol (226) 48
Figure 38. Diethyl dimethylpyrophosphonate (230) 49
Figure 39. S-[2-(Diisopropylamino) ethyl]methylphosphonothiolate (239) 50
Figure 40. N,N'-Dicyclohexylthiourea (240) 51
Figure 41. 3,6,9-Trithia-1,11-undecanediol (242) 52
Figure 42. Diisopropyl dichloromethylphosphonate (248) 53
Figure 43. Ethyl phosphoric tetramethylphosphorodiamidic anhydride (260) 54
Figure 44. Diethyl phosphoric ethyl hydrogen phosphoric anhydride (262) 55
Figure 45. O-Ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothiolate (VX) (267) 56
Figure 46. 6-Oxa-3,9,12-trithia-1,4-tetradecanediol (286) 57
Figure 47. Bis(tetramethylphosphorodiamidic) anhydride (286) 58
Figure 48. Ethyl dimethylphosphoramidic tetramethylphosphoamidic anhydride (287) 59

Figure 49. Bis[2-(diisopropylamino)ethyl] sulfide (288) 60

Figure 50. Bis(ethyl dimethylphosphoramidic) anhydride (288) 61

Figure 51. Diethyl phosphoric tetramethylphosphorodiamidic anhydride(288) 62

Figure 52. Diethyl phosphoric ethyl dimethylphosphoramidic anhydride (289)..... 63

Figure 53. Bis(diethyl phosphoric) anhydride (TEPP) (290) 64

Figure 54. Diethyl phosphoric ethyl isopropyl phosphoric anhydride (304)..... 65

Figure 55. Bis[2-diisopropylamino)ethyl] disulfide (320) 66

Figure 56. O-Ethyl-S-[5-(diisopropylamino)-3-thiapentyl] methylphosphonothiolate (327)..... 67

Figure 57. Diisopropyl phosphoric ethyl isopropyl phosphoric anhydride (332)..... 68

Figure 58. Bis(diisopropylphosphoric) anhydride (346) 69

Figure 59. Octamethyltetramidotriphosphoric acid (or isomer) (366) 70

Figure 60. O-Ethyl-S[8-(diisopropylamino)-3,6-dithiaoctyl] methylphosphonothiolate (387)... 71

List of tables

Table 1. Compounds identified in contaminated snow by LC-ESI-MS (23)..... 5

Table 2. Principal compounds identified in munitions-grade tabun sample (24). 6

Table 3. Lower mass product ions observed during chemical warfare agent analysis by LC-ESI-MS. 9

Table 4. Typical high resolution ESI-MS data acquired for compounds identified in the contaminated snow sample. (Sampling cone voltage: 20 volts) (23)..... 10

Table 5. High resolution ESI-MS data for two compounds identified in a failed tabun synthesis sample (Sampling cone voltage: 40 volts) (26)..... 11

Introduction

Canada, one of more than 140 countries to ratify the Chemical Weapons Convention, complies with this treaty by maintaining only small stocks of chemical warfare agents at Defence Research Establishment Suffield (DRES) for defensive research and development. DRES maintains the Canadian National Single Small-Scale Facility and provides the Canadian Forces and other National interests with a laboratory based identification capability for chemical warfare agents, degradation products and related compounds. Analyses of this type requires the use of sensitive, specific analytical methods, particularly when unambiguous proof is required for the presence of chemical warfare agents. These analytical demands are being actively addressed by DRES through the development and application of new analytical methods for the detection and identification of chemical warfare agents in a variety of samples.

Gas chromatography (GC) has been used extensively for the separation and identification of chemical warfare agents, with gas chromatography-mass spectrometry (GC-MS) being used frequently for the characterization of these compounds (1,2). GC-MS, while suitable for the direct analysis of organophosphorus chemical warfare agent in organic extracts, is usually not preferred for the direct analysis of aqueous samples or extracts since these samples normally require additional sample handling steps and derivatization prior to analysis. LC-ESI-MS is being used increasingly, as electrospray mass spectrometric data may be used to directly identify chemical warfare agents, degradation products and related compounds in collected aqueous samples or extracts. Increasingly researchers have developed atmospheric pressure ionization (e.g., electrospray (ESI), ionspray and atmospheric pressure chemical ionization) methods for the characterization of polar pesticides (3), organophosphate esters (4), and chemical warfare agents and/or their degradation products (5-24). These ionization modes have been interfaced to liquid chromatography (LC) and capillary electrophoresis (CE), with LC-MS (9-12, 14, 15, 18-24) and CE-MS (5, 13) methods being reported for the identification of lower volatility chemical warfare agent hydrolysis products. Recently, several LC-ESI-MS papers were published on the identification of organophosphorus chemical warfare agents and their hydrolysis products in aqueous (or snow) samples (14-17, 20, 23, 24) and aqueous extracts of contaminated soil samples (21, 22) during a single analysis. LC-ESI-MS was an attractive alternative to GC-MS for aqueous analyses, as both the organophosphorus chemical warfare agents and their hydrolysis products could be analysed directly without additional sample handling and derivatization.

DRES has analysed a variety of contaminated samples by LC-ESI-MS over the past several years using a time-of-flight mass spectrometer including:

a) Hydrolysed munitions grade mustard

b) Degraded O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothiolate (VX)

c) Snow contaminated with sarin (GB)

d) Soil contaminated with sarin (GB) and soman (GD)

e) Munitions grade tabun (GA)

f) Failed synthesis of tabun (GA)

g) Synthetic standards

The ESI-MS data acquired for the chemical warfare agents, degradation products and related compounds during these analyses were obtained with a resolution of 5000 (50% valley definition) in the continuum mode at several sampling cone voltages. At lower sampling cone voltages (typically 20 volts) the mass spectra were dominated by protonated, sodiated and protonated acetonitrile adducts and/or their dimers that could be used to confirm the molecular mass of each compound. Structural information was obtained by inducing product ion formation in the ESI interface at higher sampling cone voltages (typically 30 volts or more). Representative data obtained at both lower and higher sampling cone voltages for each compound were selected for entry into the DRES ESI-MS Database as part of a database collaboration between Canada (DRES) and The Netherlands (TNO Prins Maurits Laboratory) (25).

Experimental

ESI-MS data were acquired using a Micromass LCT time-of-flight mass spectrometer equipped with the Z-spray electrospray interface. The electrospray capillary was operated at 3.2 kV with sampling cone voltages in the 20 to 70 volt range. Nitrogen desolvation gas was introduced into the interface (80 °C) at a flow rate of 480 L/h. Nitrogen nebulizer gas was introduced at a flow rate of 66 L/h. ESI-MS data were generally acquired from 700 to 70 Da (1 sec) in the continuum mode with a resolution of 5000 (50% valley definition).

LC separations were performed using an Applied Biosystems Model 140B dual syringe pump equipped with a Micro-Tech 150 mm × 0.32 mm I.D. C_{18} (Zorbax, 5 µm) packed fused-silica capillary column and a Rheodyne 8125 injector with a 5 µL sample loop. The following solvent compositions were prepared for LC separation: Solvent A (0.1% trifluoroacetic acid in water) and Solvent B (0.1% trifluoroacetic acid in acetonitrile (ACN)/water, 95:5). Chromatographic separations were performed using a 1% to 75%B gradient program over 30 (or 45) minutes or a 1% to 40%B gradient program over 30 minutes. In order to minimize dead volume effects and ensure reproducible mixing, the mobile phase was delivered at 200 µL/min and split prior to the injector such that the flow through the column was 16 µL/min.

Results and Discussion

The DRES ESI-MS Database contains the mass spectra of 60 chemical warfare agents, degradation products and related compounds acquired during the analysis of chemical munitions fills, synthetic mixtures and contaminated environmental samples. The mass spectra, illustrated in Figures 1 to 60, have been compiled in order of increasing molecular mass and contain ESI-MS data acquired at two sampling cone voltages for each compound.

LC-ESI-MS separations

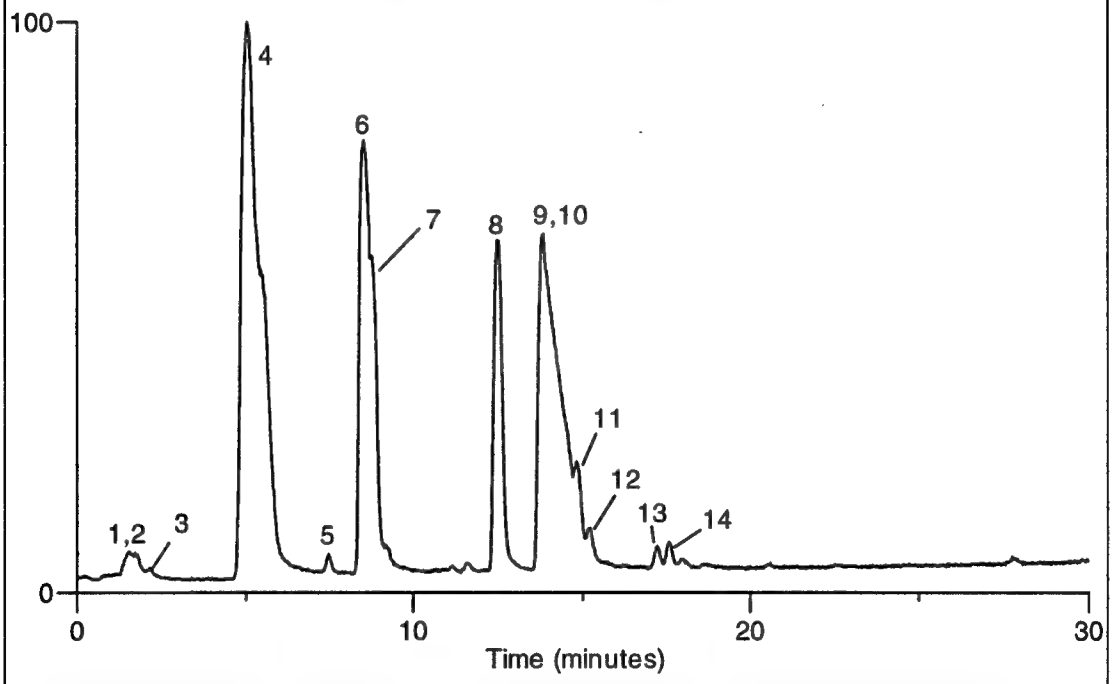
Collected environmental and other samples typically contain multiple components and require chromatographic separation prior to MS characterization of each individual component. Capillary column GC-MS remains the method of choice for the analysis of many contaminated organic extracts, with electron impact ionization being used most frequently for the characterization of each compound (1,2). However this separation technique does not generally permit direct analysis of contaminated aqueous samples or extracts and requires a derivatization step prior to the analysis of many of the more polar chemical warfare agent degradation products. Increasingly, researchers have turned to LC-ESI-MS (14-17, 20, 23, 24) for the analysis of chemical warfare agents and their degradation products in aqueous samples, as this technique allows for the identification of these compounds in aqueous samples during a single analysis.

Several acetonitrile/water gradient programs were established to facilitate LC separation of the aqueous sample components in the samples studied. Flow rates, ranging from 10 to 20 µL/min were evaluated, with 16 µL/min being selected as a comprise, offering good chromatographic peak shape and component separation in a reasonable analysis time. Most samples contained multiple components, with the snow sample contaminated with sarin (Table 1) and the munitions grade tabun sample (Table 2) being typical. Upwards of a dozen sample components were readily identified and characterized in both examples by LC-ESI-MS (23, 24).

LC-ESI-MS offers several advantages over GC-MS for the analysis of chemical warfare agents, degradation products and related compounds. This analytical approach allows for the analysis of most chemical warfare agents (with the exception of mustard) and their more polar degradation (e.g., hydrolysis) products during a single analysis as opposed to the two analyses typically required by GC-MS. This advantage was recently demonstrated during the analysis of aqueous extracts of several soil samples contaminated with sarin and soman (21, 22). LC-ESI-MS was used to identify sarin (Figure 6) and soman (Figure 21) as well as their hydrolysis products, isopropyl methylphosphonic acid (Figure 4) and pinacolyl methylphosphonic acid (Figure 15). Related sample components were also readily identified in the presence of chemical warfare agents and degradation products, as illustrated by the number of compounds of similar structure characterized during LC-ES-MS analysis of the contaminated snow sample and the munitions-grade tabun sample, respectively (Tables 1 and 2).

Table 1. *Compounds identified in contaminated snow by LC-ESI-MS (23).*

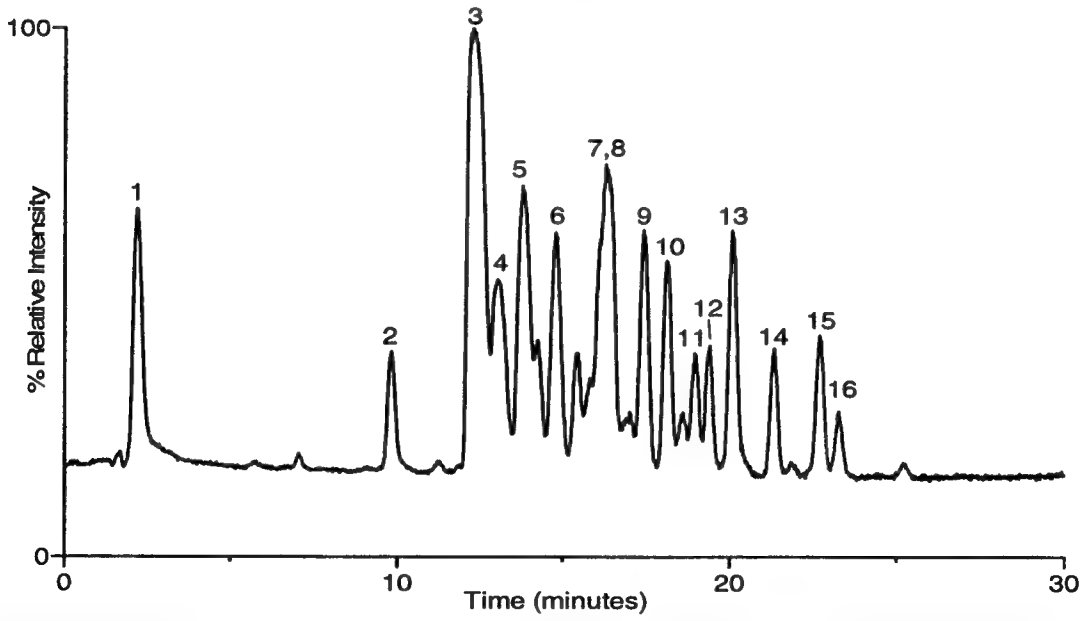
LC-ESI-MS Peak #	Compound Name	MW
1	Methylphosphonic acid	96
2	Methylphosphonofluoridic acid	98
3	Dimethylphosphinic acid	94
4	Isopropyl methylphosphonic acid	138
5	Isopropyl dimethylphosphinate	136
6	Sarin (Isopropyl methylphosphonofluoridate)	140
7	Isopropyl methyl methylphosphonate	152
8	Diisopropyl methylphosphonate	180
9	Pentyl dibutylamine	199
10	Tributylamine	185
11	Diisopropyl chloromethylphosphonate	214
12	Diisopropyl phosphorofluoridate	184
13	Triisopropyl phosphate	224
14	Diisopropyl dichloromethylphosphonate	248



LC-ESI-MS total-ion-current (600 to 85 Da) chromatogram obtained for the snow sample with a sampling cone voltage of 20 volts. Gradient program: 1% to 75%B in 30 minutes.

Table 2. *Principal compounds identified in munitions-grade tabun sample (24).*

LC-ESI-MS Peak #	Compound Name	MW
1	Ethyl dimethylphosphoramidic acid	153
2	Tetramethylphosphordiamidic cyanide	161
3	Ethyl dimethylphosphoramidocyanidate (tabun)	162
4	Ethyl tetramethylphosphoramidate	180
5	Diethyl dimethylphosphoramidate	181
6	Triethyl phosphate	182
7	Diethyl phosphoric ethyl dimethylphosphoramidic anhydride	289
8	Ethyl isopropyl dimethylphosphoramidate	195
9	Diethyl isopropyl phosphate	196
10	Diethyl phosphoric isopropyl dimethylphosphoramidic anhydride (or isomer)	303
11	Diisopropyl ethyl dimethylphosphoramidate	209
12	Diethyl phosphoric ethyl isopropyl phosphoric anhydride	304
13	Diisopropyl ethyl phosphate	210
14	Diethyl phosphoric diisopropyl phosphoric anhydride (or isomer)	318
15	Triisopropyl phosphate	224
16	Diisopropyl phosphoric ethyl isopropyl phosphoric anhydride	332



LC-ESI-MS total-ion-current (700 to 70 Da) chromatogram obtained for the munitions-grade tabun sample with a sampling cone voltage of 30 volts. Gradient program: 1% to 75%B in 45 minutes.

LC-ESI-MS sensitivity

The time-of-flight mass spectrometer instrument offers a significant improvement in sensitivity over the older DRES Autospec-Q instrument for the acquisition of complete electrospray mass spectra. The sensitivity of the LC-ESI-MS method was estimated with triethyl phosphate (Figure 20), a compound that does not readily hydrolyse in water. A complete interpretable mass spectrum (sampling cone voltage: 20 volts) was obtained for 50 pg of TEP during LC-ESI-MS analysis. The S/N ratio for the m/z 183, $(M+H)^+$, reconstructed ion current chromatogram was approximately 25:1 (24).

The relative sensitivities of LC-ESI-MS (time-of-flight) and GC-MS (quadrupole) during the acquisition of full mass spectra were investigated with a synthetic sample that failed to produce tabun (26). A 5 µL aliquot of the synthetic sample was diluted to 30 mL with water for LC-ESI-MS analysis and to 30 mL of dichloromethane for GC-MS analysis. LC-ESI-MS (5 µL injection volume) sample sensitivity for the acquisition of a full mass spectrum was comparable to GC-MS (1 µL injection volume) for the compounds detected by both techniques. Similar S/N ratios in the total-ion-current were observed for trace components (low to subnanogram quantities) in the sample using the injection volumes indicated. Twelve sample components were identified by LC-ESI-MS, while only ten were detected by GC-MS. The two sample components that were not detected, ethyl phosphoric tetramethylphosphorodiamidic anhydride (Figure 43) and octamethyltetramidotriphosphoric acid (Figure 59), were not detected by GC-MS due to their polarity. Derivatization and a second analysis would be required for GC-MS analysis of these compounds.

ESI-MS mass spectral differences

ESI data may be acquired at different sampling cone voltages. At lower sampling cone voltages (e.g., 20 volts) the acquired mass spectra contain molecular mass information in the form of MH^+, $[MH+ACN]^+$ ions and/or protonated dimers, while higher sampling cone voltages (e.g., 30 to 70 volts) will reduce the relative intensity of the MH^+ and enhance the formation of structurally important product ions in the ESI interface. GC-MS data acquired under electron impact ionization generally contain a larger number of structurally significant fragmentation ions, but often these mass spectra do not contain a molecular ion that may be used to establish the molecular mass of the compound. In these cases a second GC-MS analysis under chemical ionization conditions would be required to establish the molecular mass of the identified compound.

Organophosphorous chemical warfare agents and related compounds containing alkoxy substituents generally exhibit ESI-MS product ions due to alkene loss from the alkoxy substituents (and their acetonitrile adducts) at higher sampling cone voltages. Diisopropyl methylphosphonate (Figure 16), an organophosphorus compound identified in a snow sample contaminated with sarin (23), was typical, exhibiting product ions at m/z 139 and m/z 97 due to sequential loss of C_3H_6 from the MH^+ ion.

A common degradation product in VX, bis[2-(diisopropylamino)ethyl] disulfide (Figure 55), was characterized with sampling cone voltages of 20 and 50 volts. Molecular mass was established by the presence of a well resolved $[MH_2]^{2+}$ isotopic cluster and a MH^+ ion at m/z 161 (rounded up to nominal mass) and m/z 321, respectively. Bis[2-(diisopropylamino)ethyl] disulfide, one of a series of compounds of the general form, $(iPr)_2NC_2H_4S_nC_2H_4N(iPr)_2$ (where n=1,2,3), exhibited a number of characteristic product ions due to loss of $HS_2C_2H_4N(iPr)_2$, $HSC_2H_4N(iPr)_2$ and $HN(iPr)_2$ from the MH^+ ion at the higher sampling cone voltage.

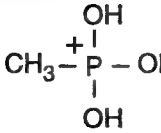
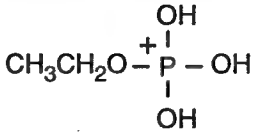
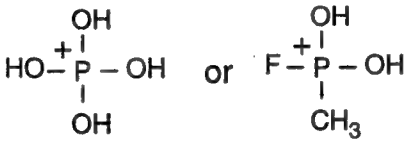
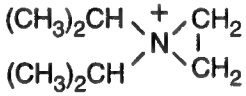
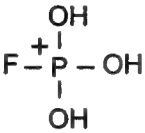
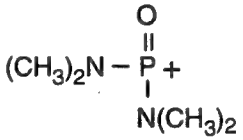
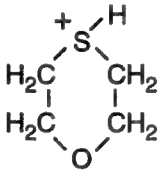
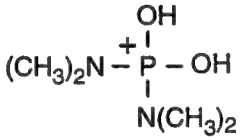
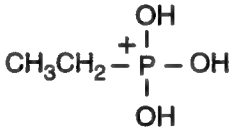
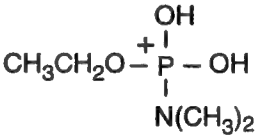
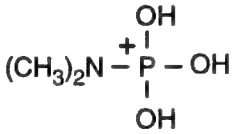
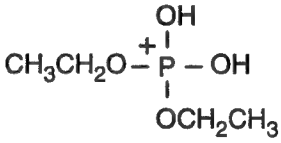
Hexamethylphosphorotriamide (Figure 13), a product observed in the failed tabun synthetic sample (26) produced only one significant product ion at a higher sampling cone voltage. An ion at m/z 135, due to loss of $HN(CH_3)_2$) from the MH^+ ion, was observed for this and several other similar amides.

The hydrolysis products of munitions grade mustard included a number of longer chain diols. Diol ESI-MS data contained both molecular ion and product ion content, enabling structural identification of these hydrolysis products. The ESI-MS data obtained for 6-oxa-3,9-dithia-1,11-undecanediol (Figure 37), the hydrolysis product of bis[(2-chloroethylthio)ethyl]ether (T), was typical. The mass spectrum contained a significant MH^+ ion at m/z 227 and a M_2H^+ ion at m/z 453. 6-Oxa-3,9-dithia-1,11-undecanediol exhibited a product ion due to loss of H_2O at m/z 209 along with product ions at m/z 181, m/z 149 and m/z 105 due to $[MH-H_2O-C_2H_4]^+$, $[MH-H_2O-SC_2H_4]^+$ and $[MH-H_2O-SC_2H_4-OC_2H_4]^+$, respectively, that could be used to establish S and O positioning.

During the course of investigations a number of common lower mass product ions were observed for the organophosphorus and organosulfur compounds analysed. The presence of these ions, listed in Table 3, additional product ions and the MH^+ ion often aided in the identification of unknowns. For example, methylphosphonofluoridates such as cyclohexyl methylphosphonofluoridate (Figure 14) tend to exhibit a significant product ion at m/z 99 due to alkene loss from the alkoxy substituent, while phosphates, such as triethyl phosphate (Figure 20) will also exhibit an ion of the same nominal mass (with less relative intensity) after sequential loss of the alkenes associated with the alkoxy substituents. Similarly the presence of a significant ion at m/z 97 often indicates the presence of an alkyl methylphosphonic acid such as pinacolyl methylphosphonic acid (Figure 15) or a dialkyl methylphosphonate such as diethyl methylphosphonate (Figure 7).

Compounds related to VX, such as S-[2-(diisopropylamino) ethyl]methylphosphonothiolate (Figure 39), generally exhibit a common product ion at m/z 128 due to the presence of $-CH_2CH_2N(CH(CH_3)_2)_2$, while thiodiglycol (Figure 2) and the hydrolysis products of longer chain sulfur sulfur vesicants, such as 3,6,9-trithia-1,11-undecanediol (Figure 41) usually produce a significant protonated thioxane ion at m/z 105. Tabun related compounds, such as diisopropyl dimethylphosphoramidate (Figure 32), containing a single dimethyl amine substituent (and alkoxy substitution) produce lower mass product ions at m/z 126, while an ion at m/z 135 generally indicates an organophosphorus compound with two dimethyl amine substituents.

Table 3. *Lower mass product ions observed during chemical warfare agent analysis by LC-ESI-MS.*

m/z	Possible structures	m/z	Possible structures
97		127	
99		128	
101		135	
105		153	
111		154	
126		155	

Accurate mass measurement during LC-ESI-MS analysis may also aid in the assignment of elemental composition of both MH^+ and product ions. High resolution measurements (5000 resolution with a 50% valley) were made on all the compounds identified in the contaminated snow sample (23). Data acquired under these conditions compared favorably with theoretical data, with errors typically being less than 0.005 Da. Table 4 contains the MH^+ and selected product ion data for several of the significant sample components identified during LC-ESI-MS of this sample.

Table 4. *Typical high resolution ESI-MS data acquired for compounds identified in the contaminated snow sample. (Sampling cone voltage: 20 volts) (23).*

Compound Name	Ion	Observed Mass (Da) (mean ± SD; n = 5)	Theoretical Mass (Da)	Average Error (Da)
Methylphosphonic acid	MH^+	97.0099 ± 0.0044	97.0055	0.0044
Isopropyl methylphosphonic acid	MH^+	139.0455 ± 0.0019	139.0524	0.0069
	$[MH-C_3H_6]^+$	97.0071 ± 0.0015	97.0055	0.0016
Sarin (Isopropyl methylphosphonofluoridate)	MH^+	141.0444 ± 0.0021	141.0481	0.0037
	$[MH-C_3H_6]^+$	99.0036 ± 0.0014	99.0011	0.0025
Diisopropyl methylphosphonate	MH^+	181.1004 ± 0.0028	181.0994	0.0010
	$[MH-C_3H_6]^+$	139.0547 ± 0.0019	139.0524	0.0023
Tributlyamine	MH^+	186.2221 ± 0.0026	186.2222	0.0001
Diisopropyl phosphorofluoridate[2]	MH^+	185.0747 ± 0.0003	185.0743	0.0004
	$[MH-C_3H_6]^+$	143.0285 ± 0.0010	143.0273	0.0012
Triisopropyl phosphate	MH^+	225.1246 ± 0.0027	225.1256	0.0010
	$[MH-C_3H_6]^+$	183.0814 ± 0.0005	183.0786	0.0028

Cyclohexyl methylphosphonofluoridate (GF) (Figure 14), pinacolyl methylphosphonic acid (Figure 15), diisopropyl methylphosphonate (Figure 16) and ethyl tetramethylphosporodiamidate (Figure 17), four compounds with the same nominal mass (molecular mass of 180), produce a common MH^+ ion at m/z 181, but may be readily differentiated on the basis of their product ions. Cyclohexyl methylphosphonofluoridate exhibited the characteristic methylphosphonofluoridate ion at m/z 99, due to loss of C_6H_{10}, (and its acetonitrile adduct) at m/z 140. Both pinacolyl methylphosphonic acid and diisopropyl methylphosphonate, two compounds with identical elemental composition, exhibited the characteristic m/z 97 product ion (and its acetonitrile adduct) indicating the presence of an alkyl methyphosphonic acid or dialkyl methyphosphonate. The m/z 97 was due to loss of C_6H_{12} from the MH^+ ion of pinacolyl methylphosphonic acid, while diisopropyl methylphosphonate exhibited sequential losses of C_3H_6, resulting in an additional product ion at m/z 139. The final compound with a molecular mass of 180 Da, ethyl tetramethylphosporodiamidate, exhibited several characteristic product ions, the most significant being at m/z 153, due to loss of C_2H_4 from the MH^+ ion.

Two additional compounds with identical elemental composition, bis(ethyl dimethylphosphoramidic) anhydride (Figure 50) and diethyl phosphoric tetramethylphosphorodiamidic anhydride (Figure 51), exhibited identical mass spectra dominated by a MH^+ ion at m/z 289 under low sampling cone voltage conditions. Both anhydrides contained two ethoxy and two dimethylamine substituents based on the product ions observed. Differentiation of the two possible isomers was possible on the basis of the characteristic lower mass ions observed with a sampling cone voltage of 40 volts. Bis(ethyl dimethylphosphoramidic) anhydride exhibited ions at m/z 126 and m/z 154 indicating the

presence of both ethoxy and dimethyl amine substitution at each phosphorus atom, while the product ions at m/z 135 and m/z 153 for diethyl phosphoric tetramethylphosphorodiamidic anhydride indicated that one phosphorus contained both dimethylamine substituents. Data were obtained under high resolution conditions and Table 5 lists the elemental assignments for the ions observed during accurate mass measurement of both anhydrides (26).

Table 5. *High resolution ESI-MS data for two compounds identified in a failed tabun synthesis sample (Sampling cone voltage: 40 volts) (26).*

Compound Name	Ion	Observed Mass (Da) (mean ± SD)[2]	Theoretical Mass (Da)	Average Error (Da)
Diethyl phosphoric tetramethylphosphorodiamidic anhydride	MH^+	289.1049 ± 0.0011	289.1082	0.0033
	$[MH-C_2H_4]^+$	261.0790 ± 0.0006	261.0769	0.0021
	$[MH-HNMe_2]^+$	244.0554 ± 0.0020	244.0504	0.0050
	$[MH-(C_2H_4)_2]^+$	233.0489 ± 0.0007	233.0456	0.0033
	$[(Me_2N)_2P(OH)_2]^+$	153.0826 ± 0.0012	153.0793	0.0033
	$[(Me_2N)_2PO]^+$	135.0705 ± 0.0009	135.0687	0.0018
Bis(ethyl dimethylphosphoramidic) anhydride	MH^+	289.1064 ± 0.0011	289.1082	0.0018
	$[MH-C_2H_4]^+$	261.0753 ± 0.0015	261.0769	0.0016
	$[MH-HNMe_2]^+$	244.0517 ± 0.0021	244.0504	0.0013
	$[MH-HNMe_2-C_2H_4]^+$	229.0112 ± 0.0024	229.0143	0.0031
	$[(Me_2N)(EtO)P(OH)_2]^+$	154.0648 ± 0.0018	154.0633	0.0015
	$[(Me_2N)P(OH)_3]^+$	126.0374 ± 0.0019	126.0320	0.0054

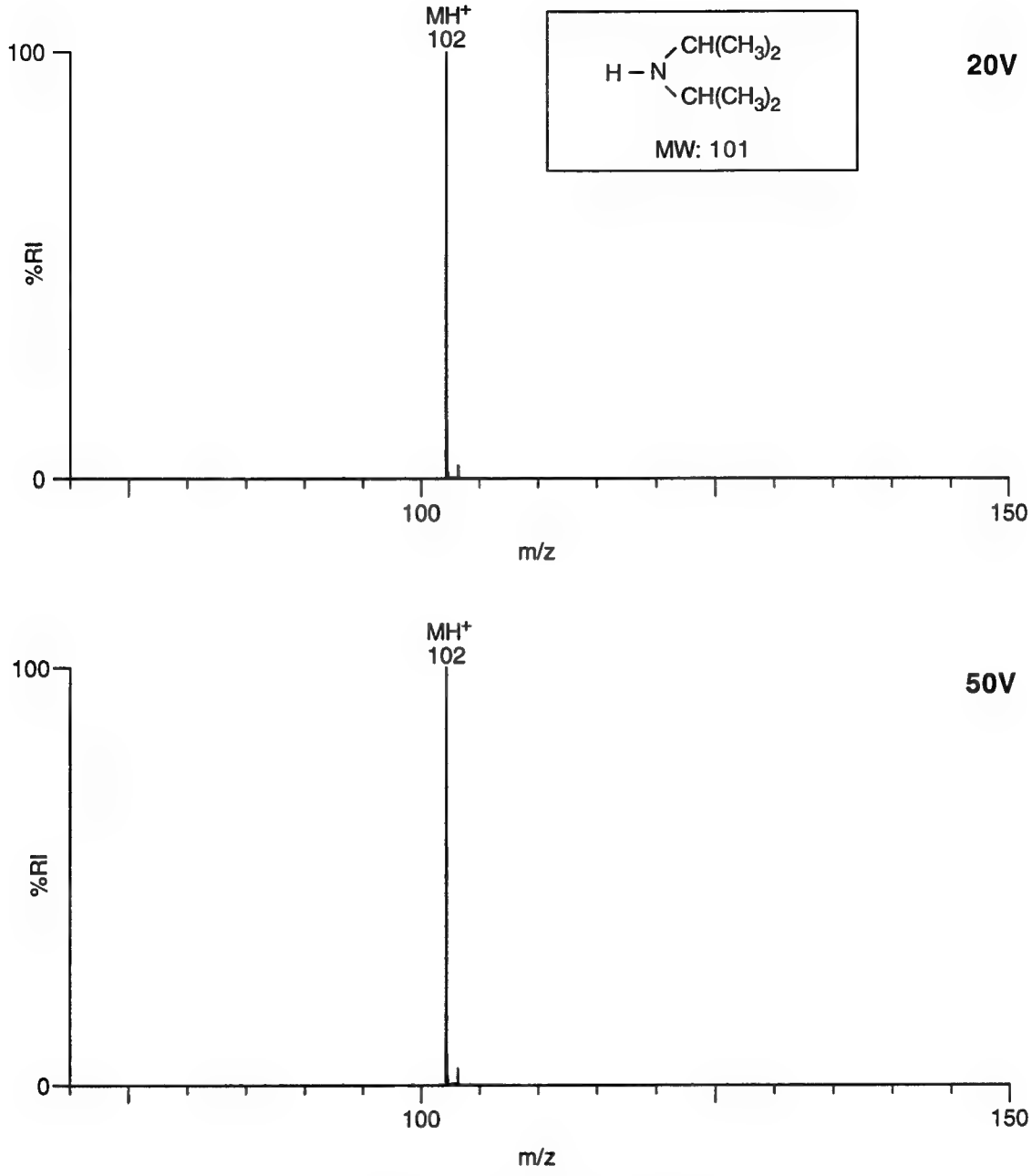


Figure 1. Diisopropylamine (101)

CAS: *108-18-9*
Formula: *$C_6H_{15}N$*
Monoisotopic MW: *101.1204*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

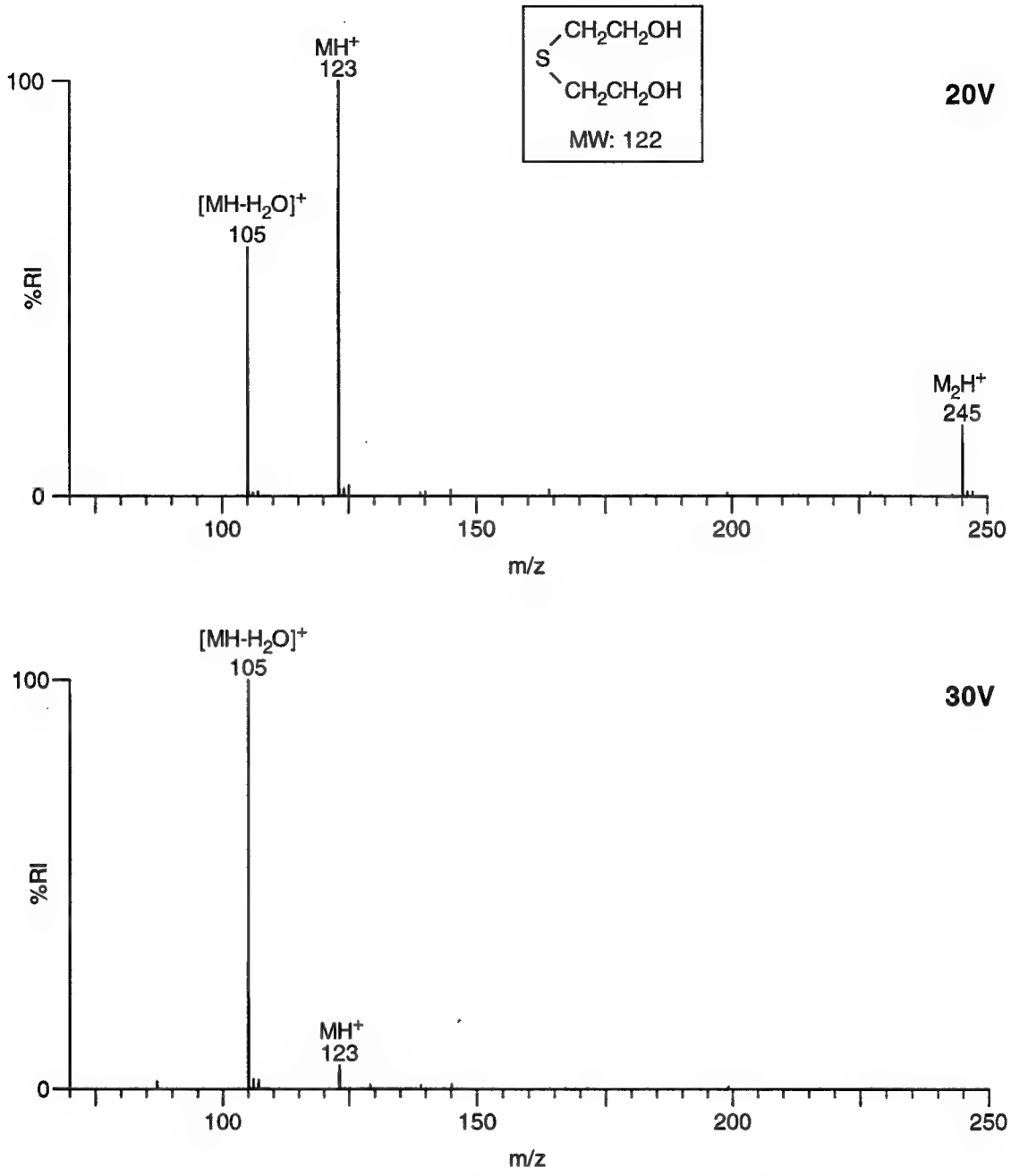


Figure 2. 2,2'- Thiodiethanol (Thiodiglycol) (122)

CAS: *111-48-8*
Formula: *$C_4H_{10}O_2S$*
Monoisotopic MW: *122.0402*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

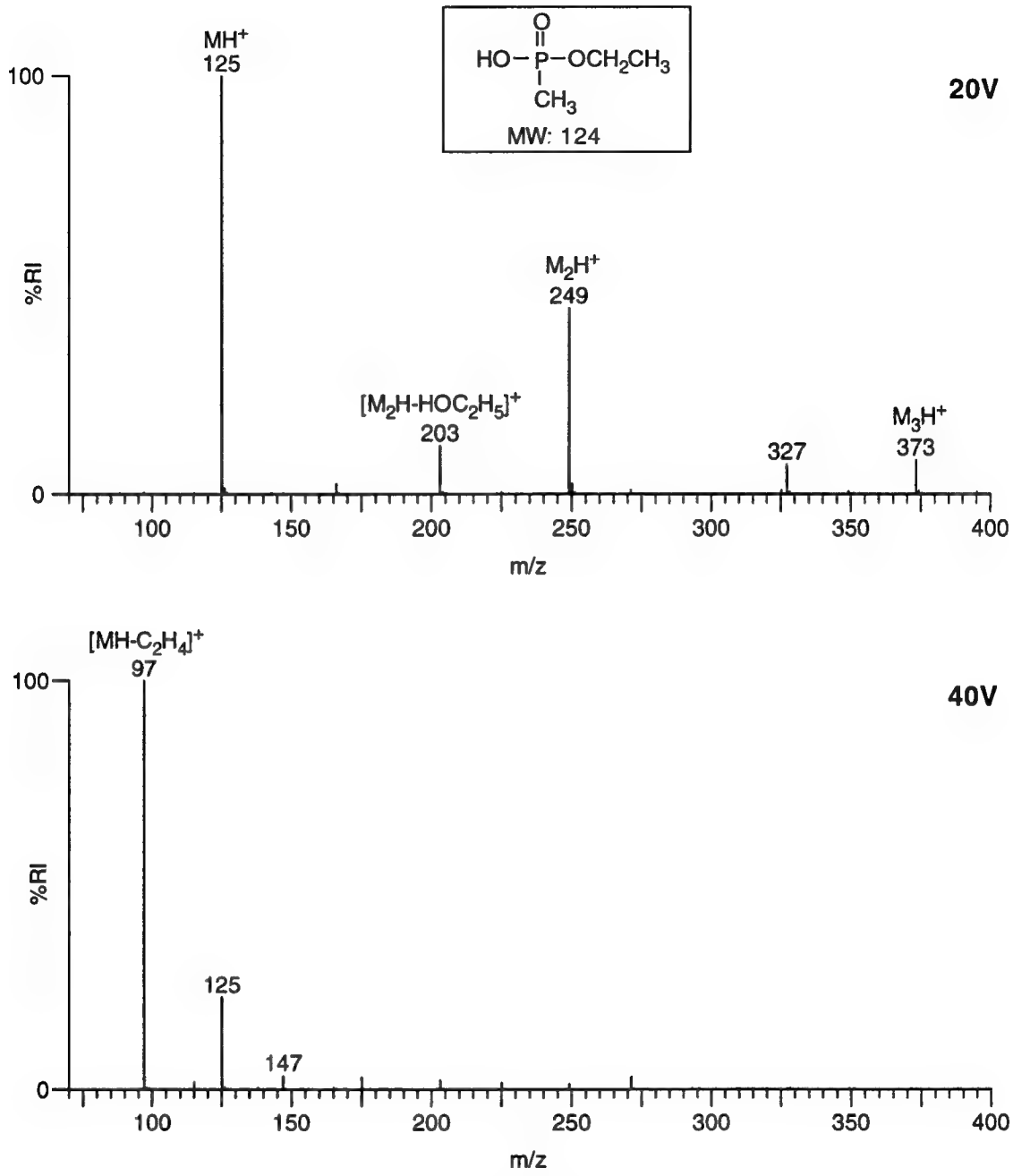


Figure 3. Ethyl methylphosphonic acid (124)

CAS: *1832-53-7*
Formula: *$C_3H_9O_3P$*
Monoisotopic MW: *124.0289*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

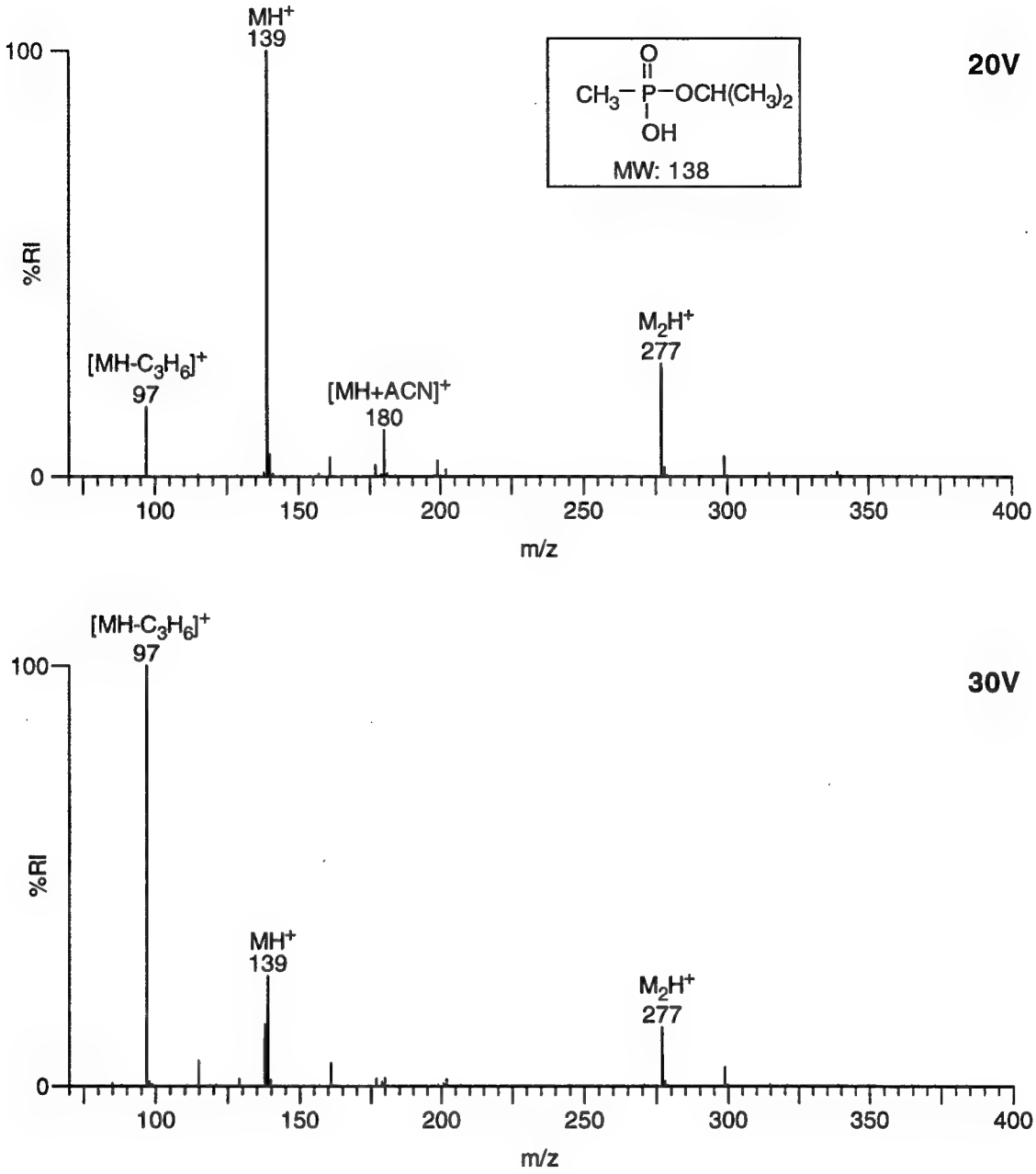


Figure 4. Isopropyl methylphosphonic acid (138)

CAS: *1832-54-8*
Formula: *$C_4H_{11}O_3P$*
Monoisotopic MW: *138.0446*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

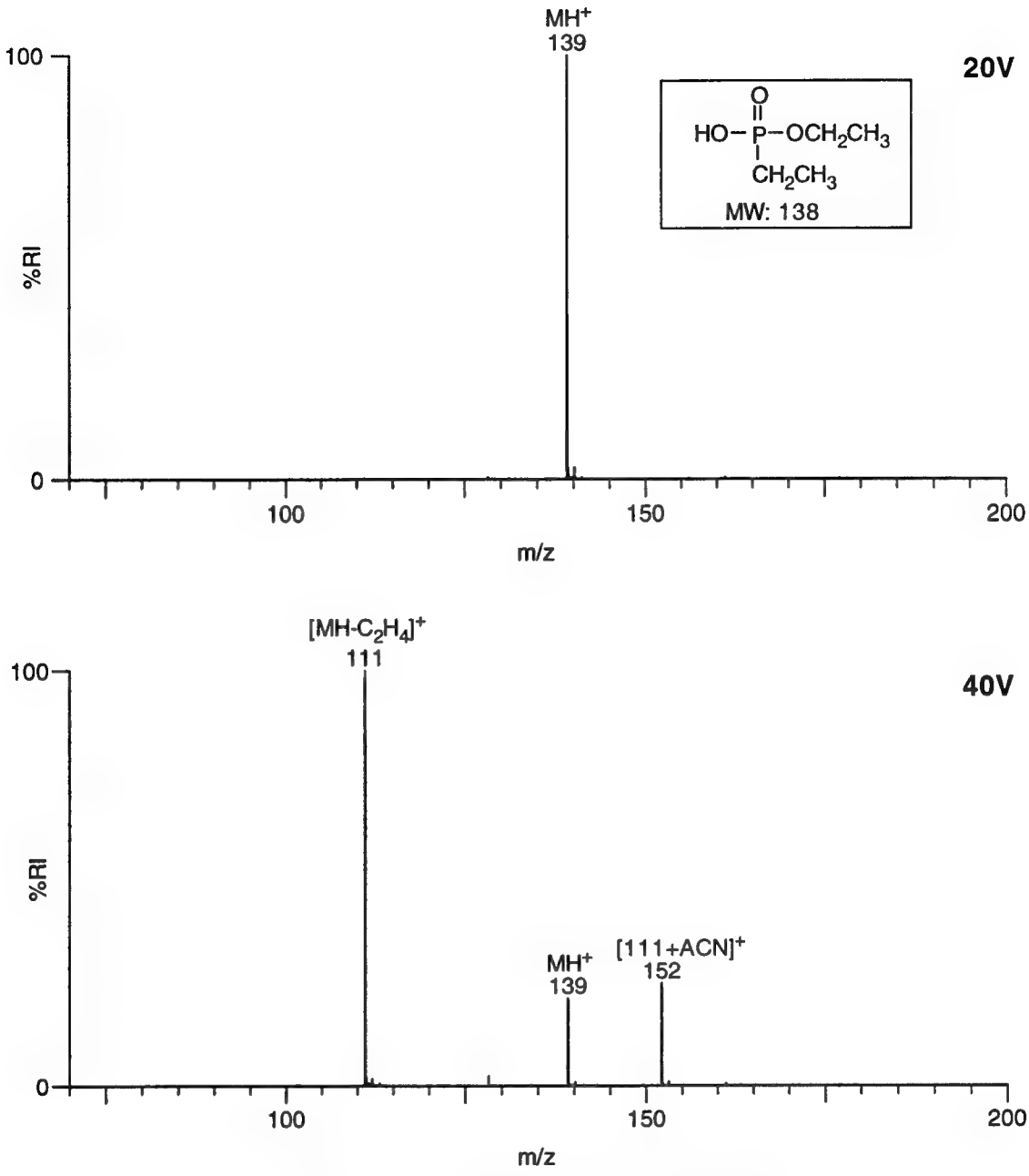


Figure 5. Ethyl ethylphosphonic acid (138)

CAS:
Formula: $C_4H_{11}O_3P$
Monoisotopic MW: *138.0446*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

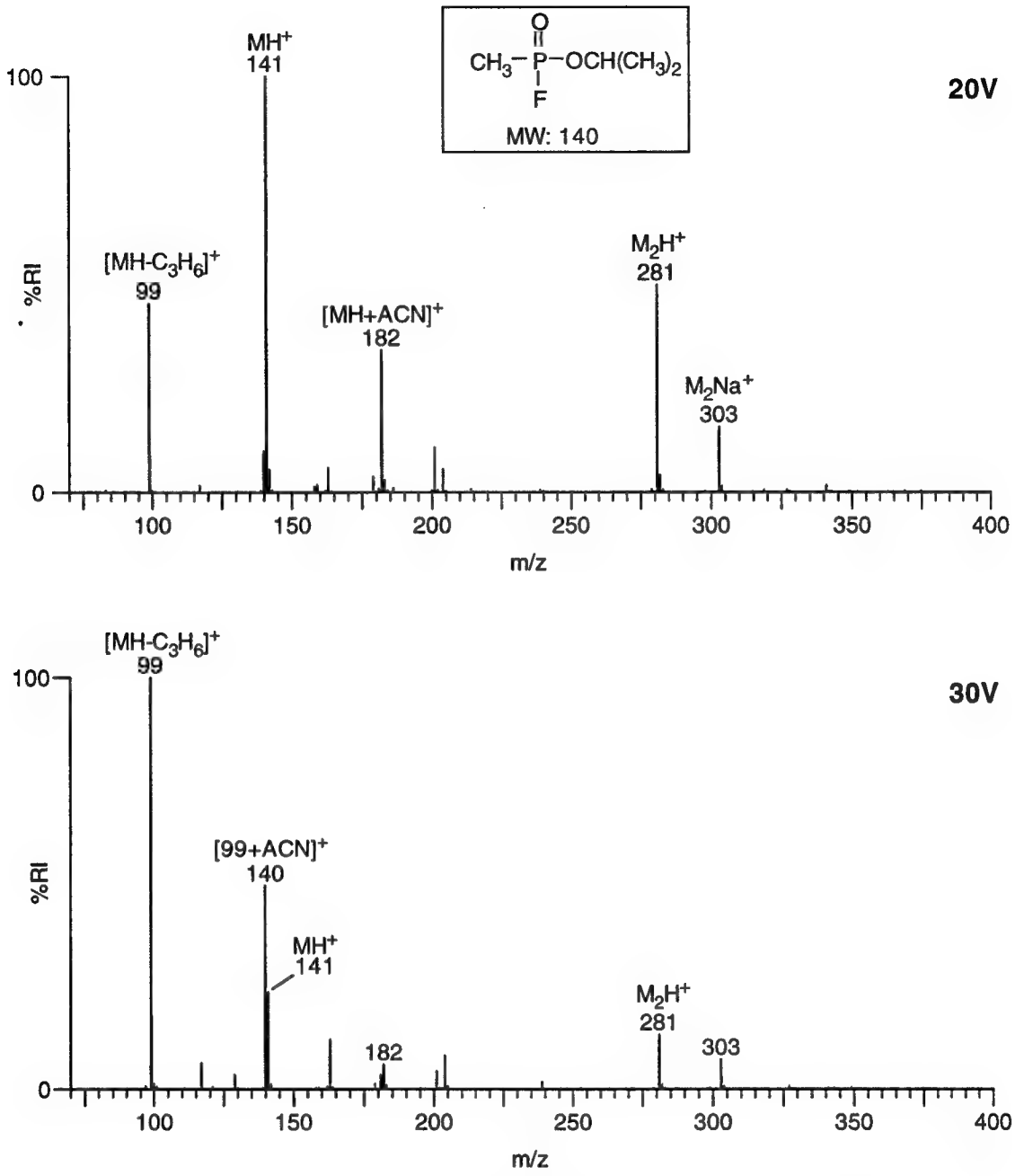


Figure 6. Isopropyl methylphosphonofluoridate (Sarin, GB) (140)

CAS: *107-44-8*
Formula: *$C_4H_{10}FO_2P$*
Monoisotopic MW: *140.0403*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

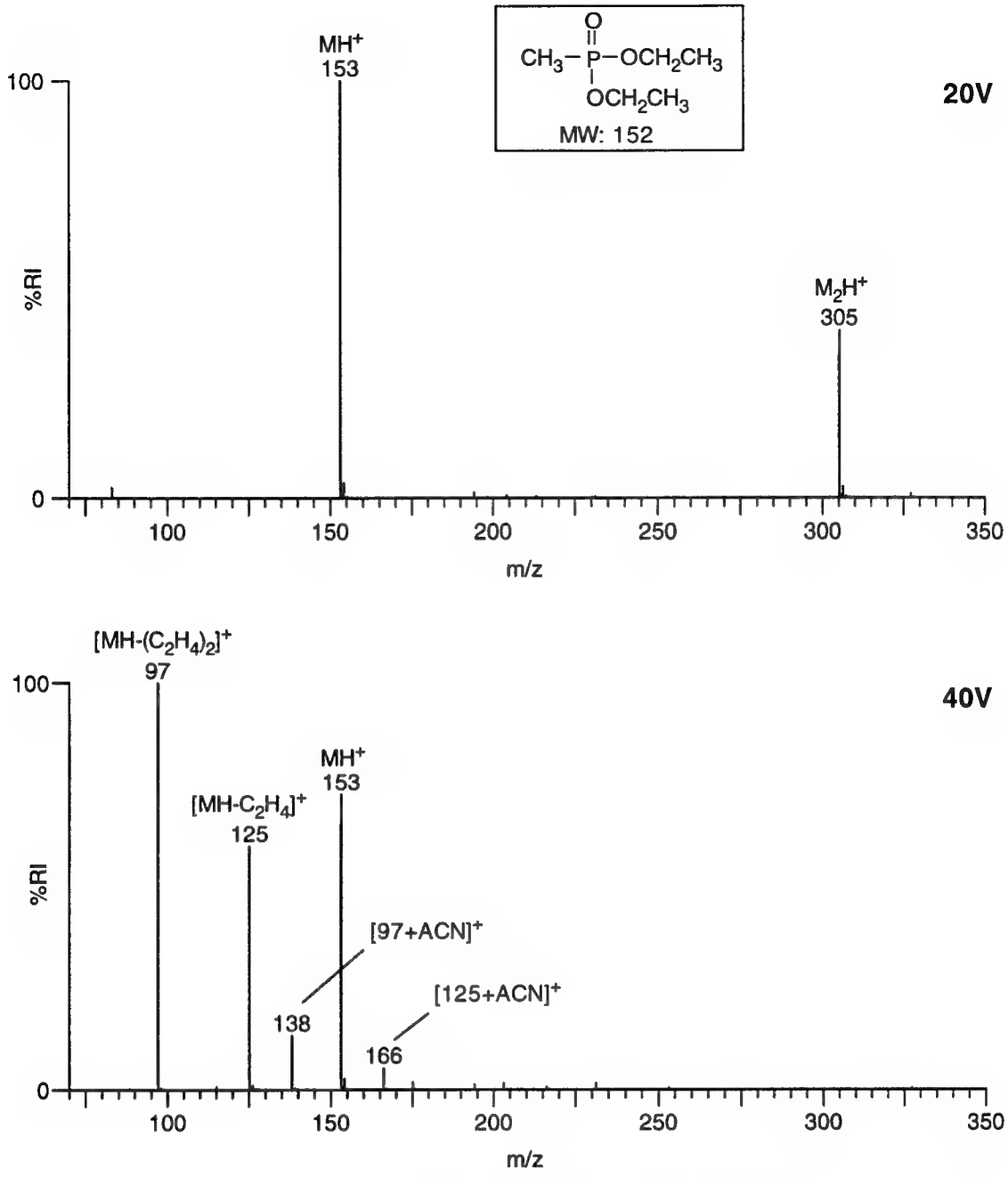


Figure 7. Diethyl methylphosphonate (152)

CAS: *683-08-9*
Formula: *$C_5H_{13}O_3P$*
Monoisotopic MW: *152.0602*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

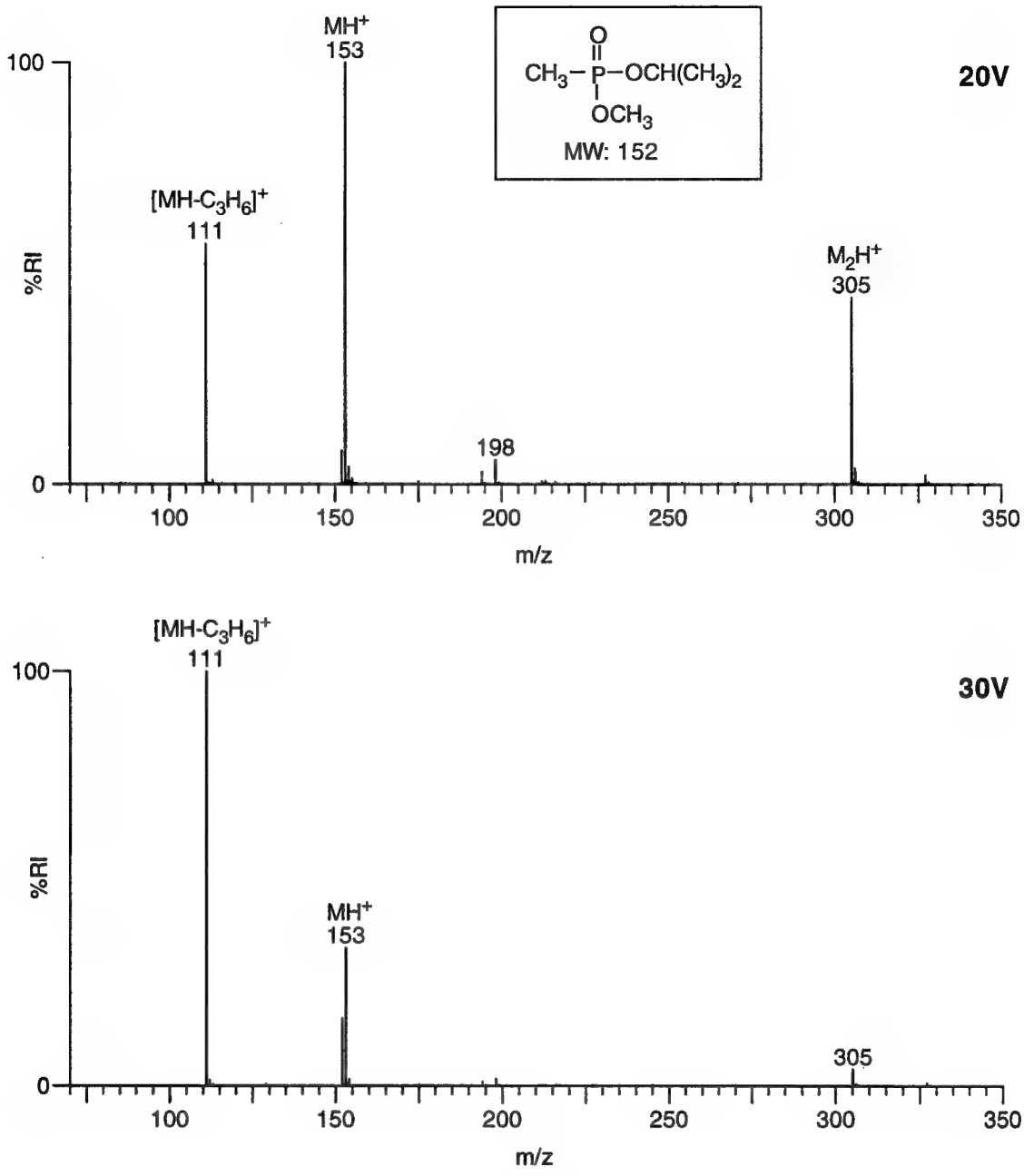


Figure 8. Isopropyl methyl methylphosphonate (152)

CAS: *690-64-2*
Formula: *$C_5H_{13}O_3P$*
Monoisotopic MW: *152.0602*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

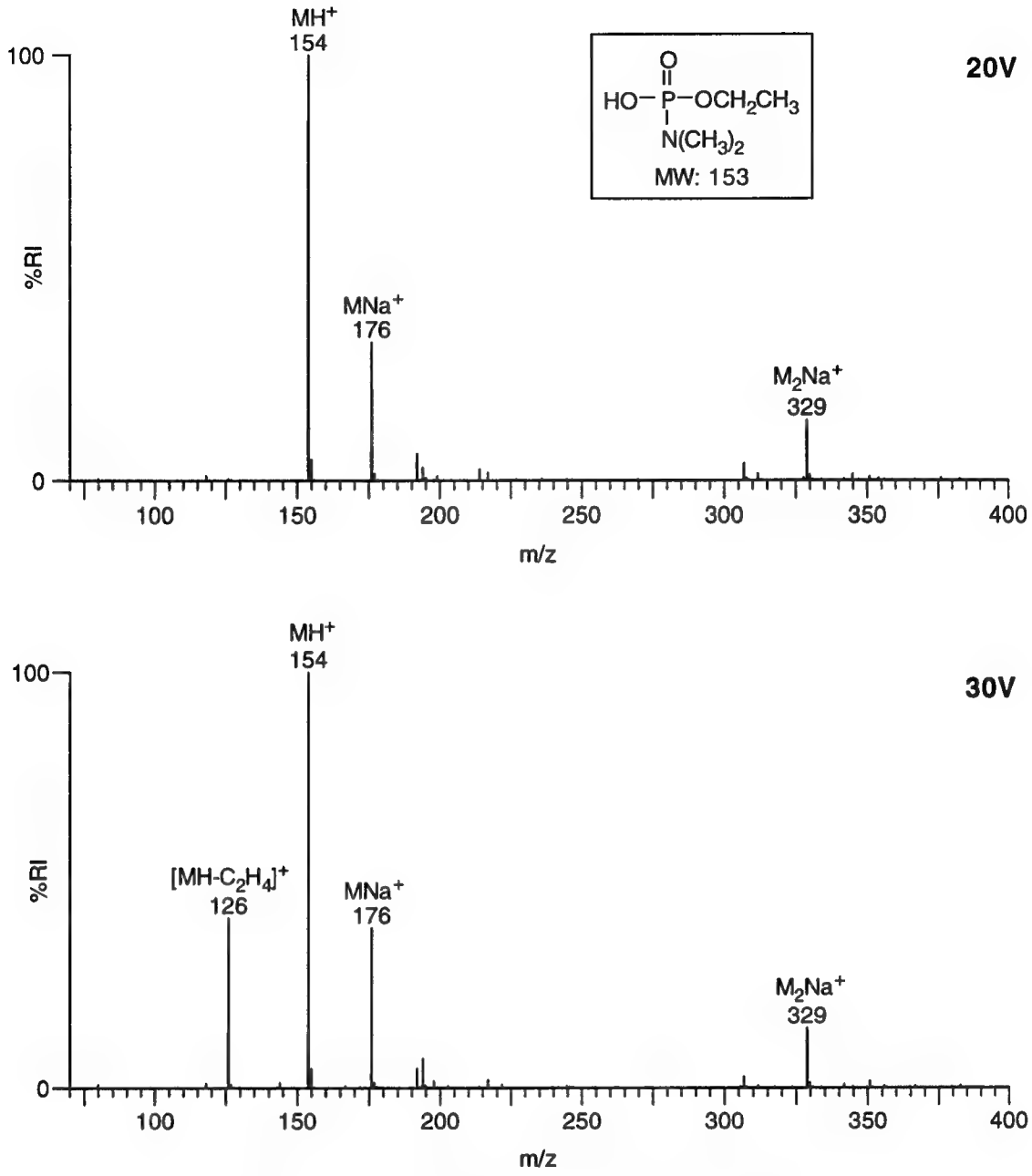


Figure 9. Ethyl dimethylphosphoramidic acid (153)

CAS: *2632-86-2*
Formula: *$C_4H_{12}NO_3P$*
Monoisotopic MW: *153.0555*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

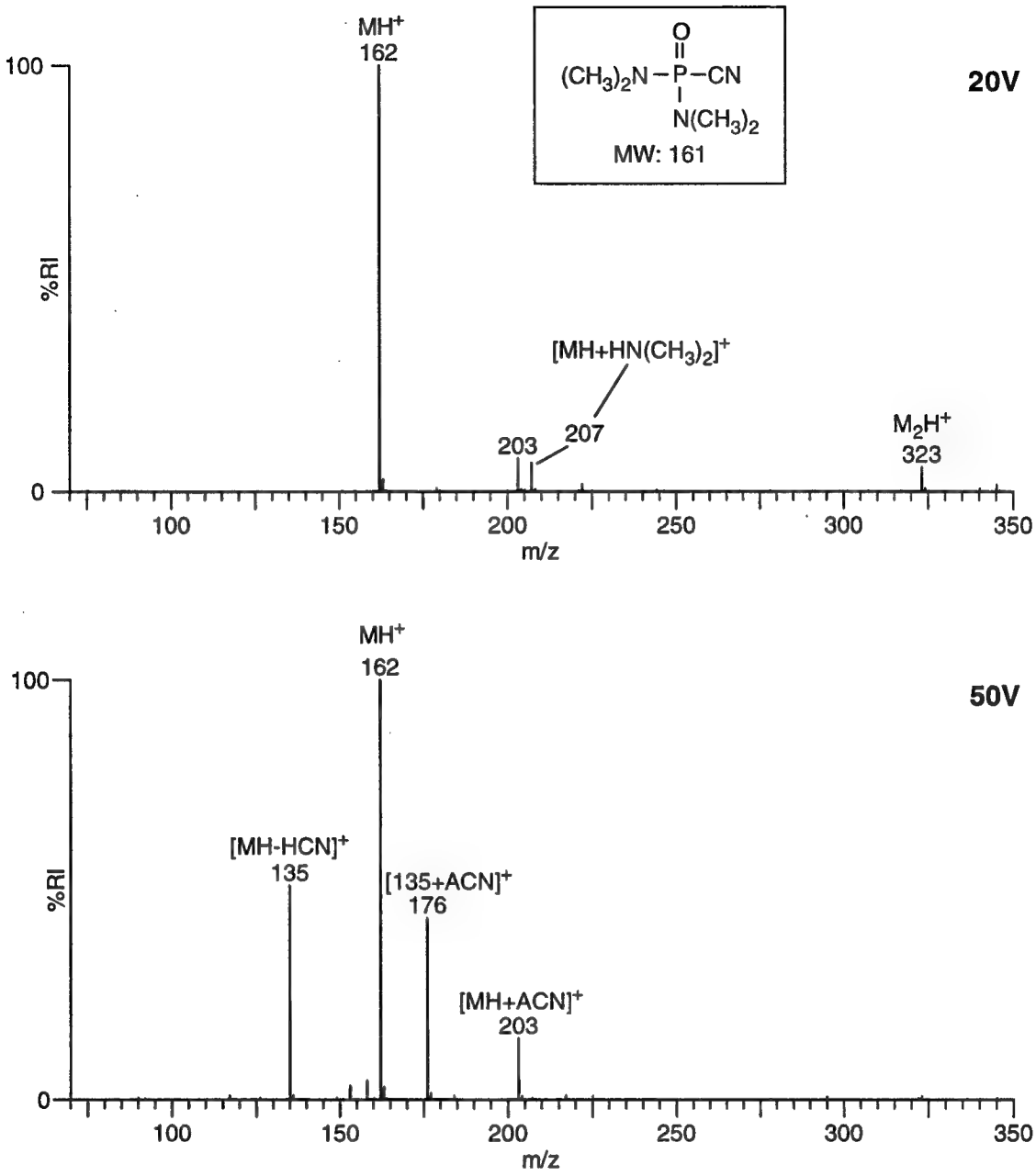


Figure 10. Tetramethyl phosphorodiamidic cyanide (161)

CAS: *14445-60-4*
Formula: *$C_5H_{12}N_3OP$*
Monoisotopic MW: *161.0718*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

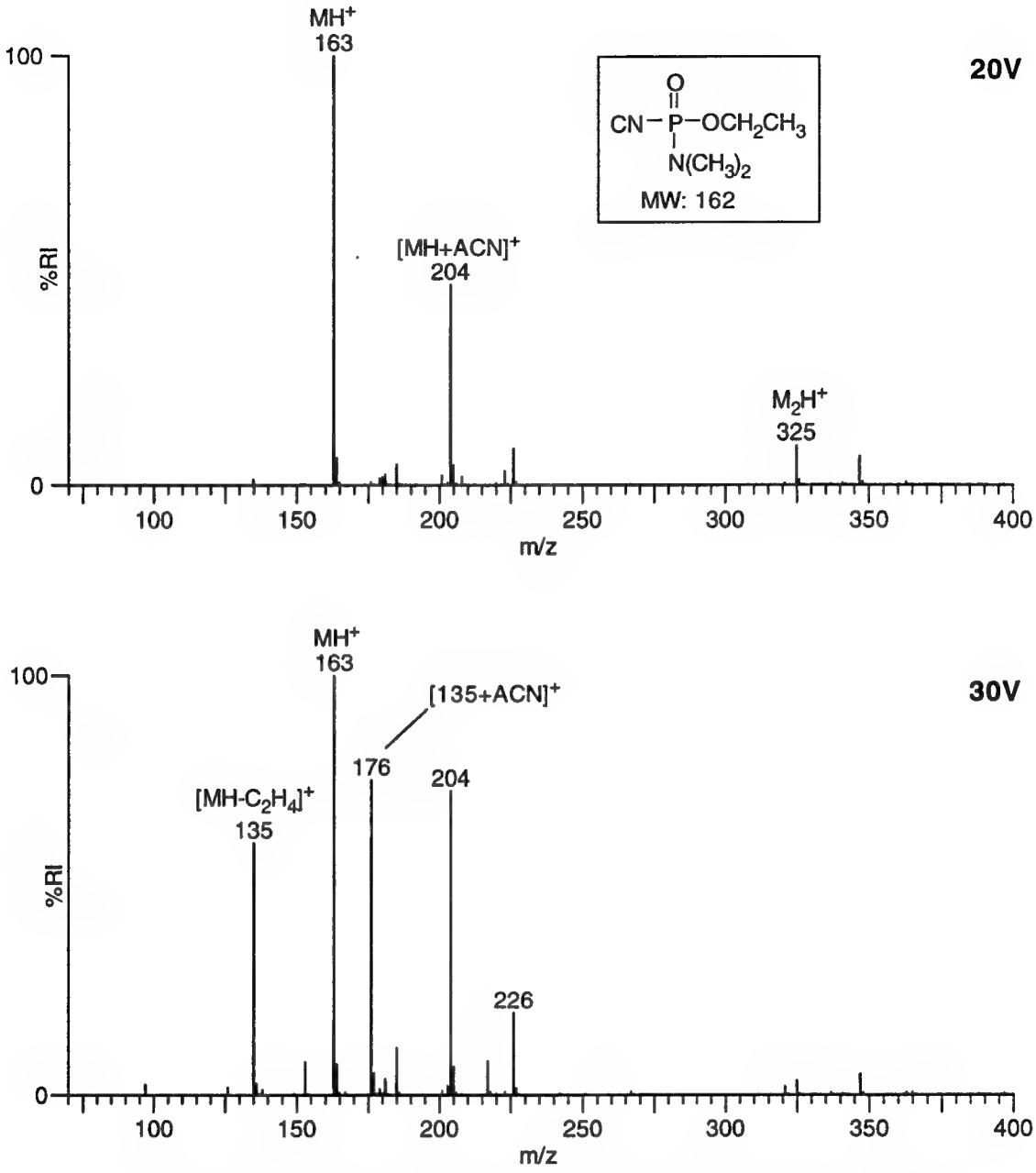


Figure 11. O-Ethyl N,N-dimethylphosphoroamidocyanidate (Tabun, GA) (162)

CAS: *77-81-6*
Formula: *$C_5H_{11}N_2O_2P$*
Monoisotopic MW: *162.00558*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

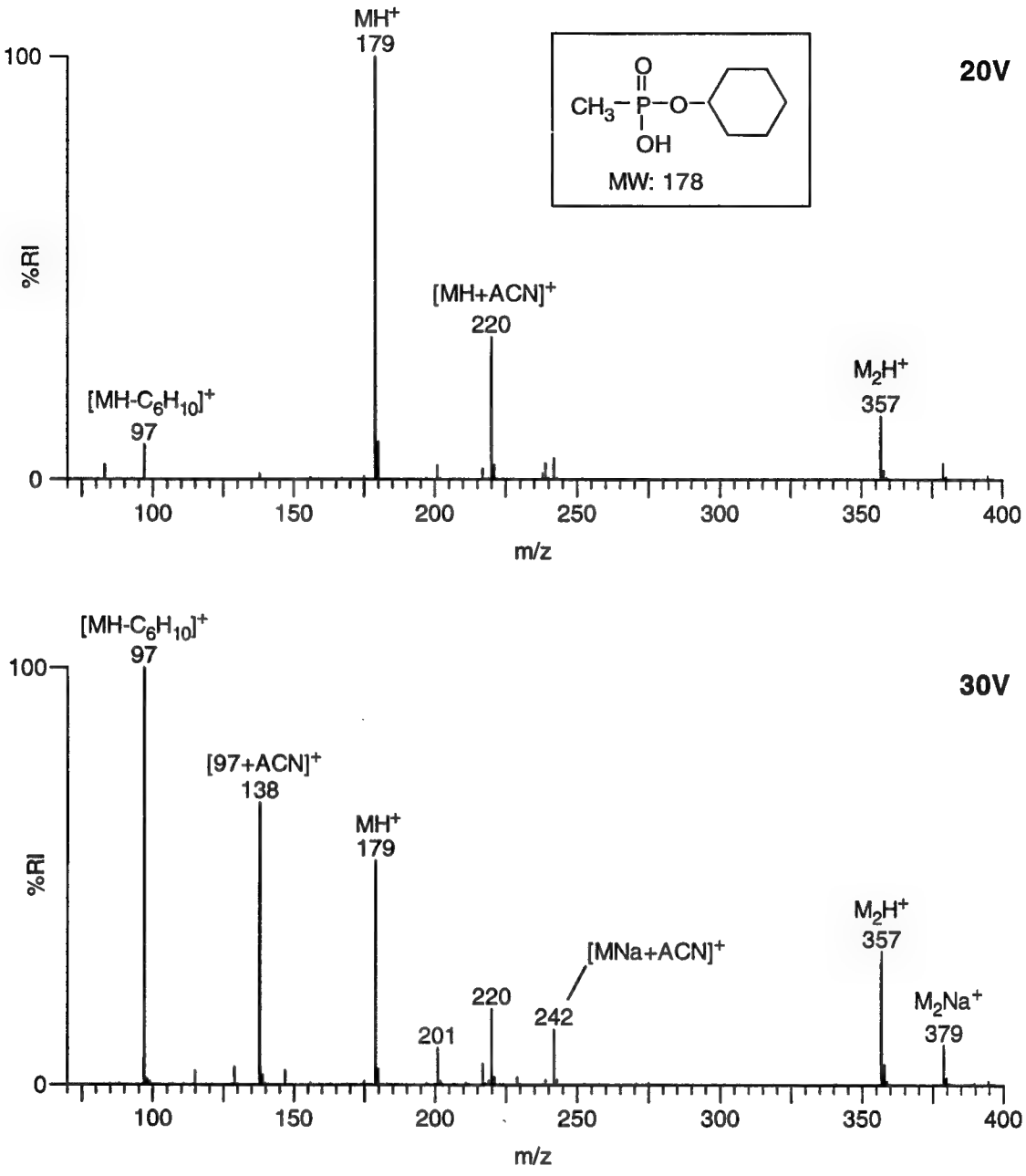


Figure 12. Cyclohexyl methylphosphonic acid (178)

CAS: *1932-60-1*
Formula: *$C_7H_{15}O_3P$*
Monoisotopic MW: *178.0759*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

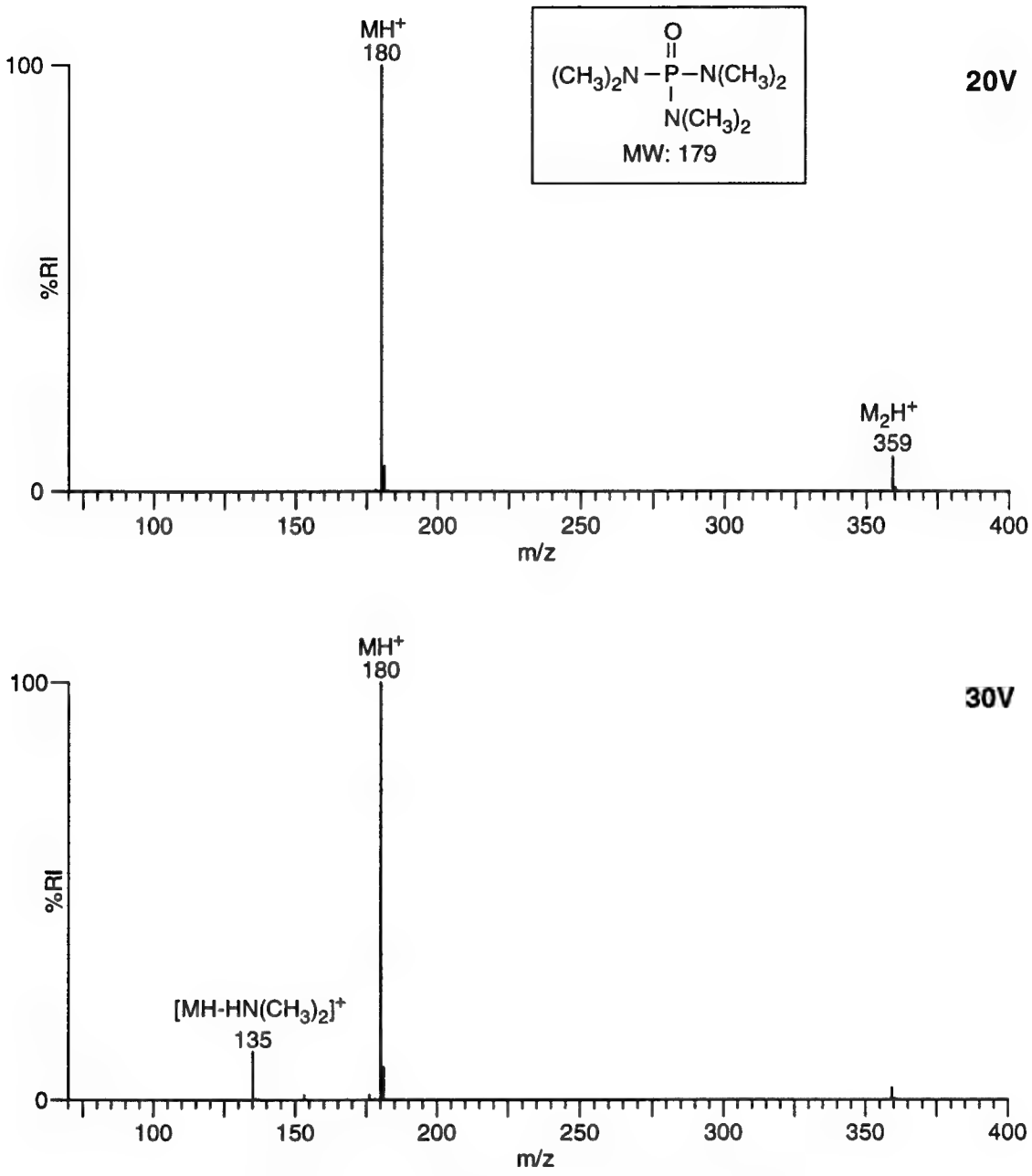


Figure 13. Hexamethylphosphorotriamide (179)

CAS: *680-31-9*
Formula: *$C_6H_{18}N_3OP$*
Monoisotopic MW: *179.1188*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

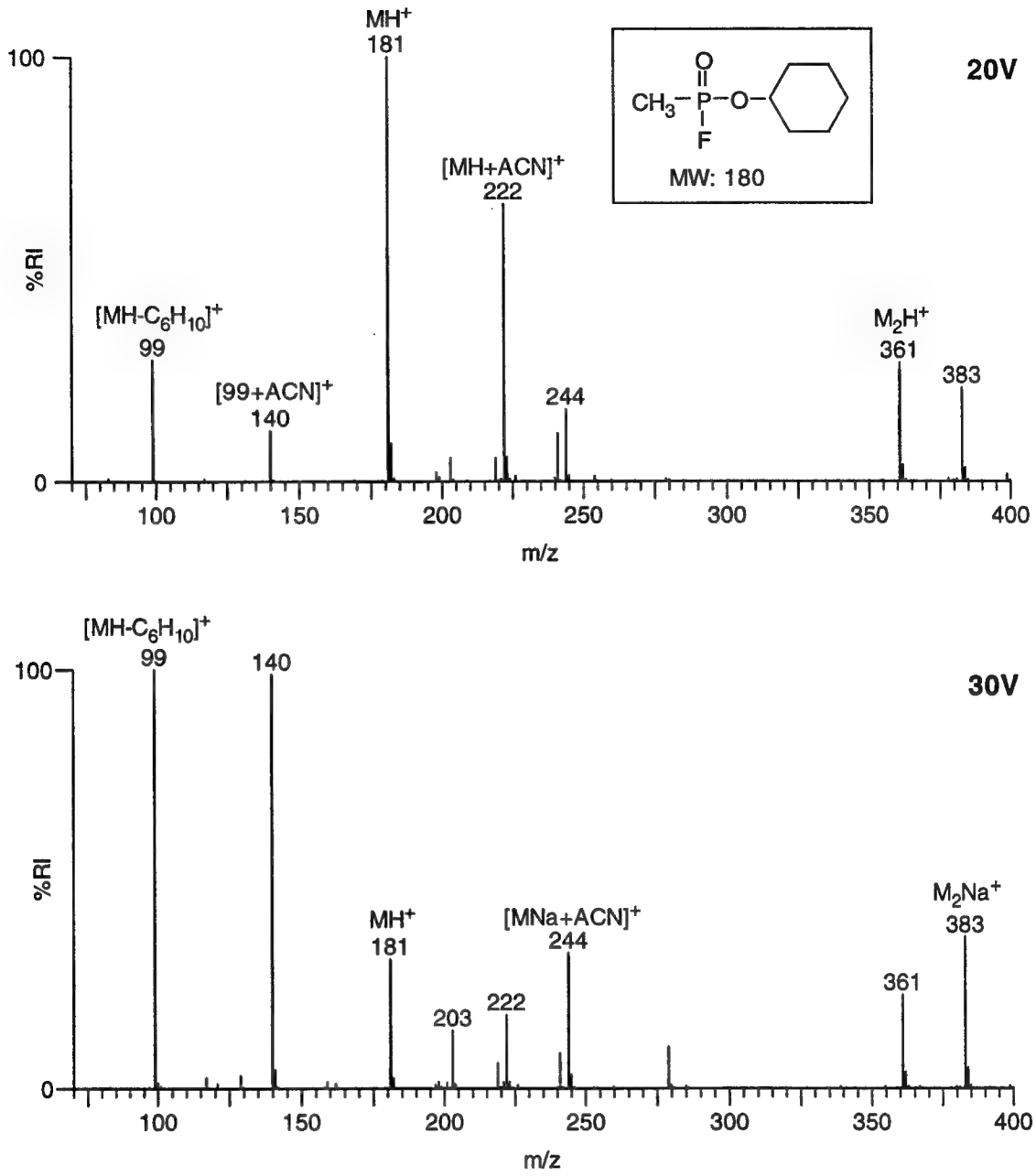


Figure 14. Cyclohexyl methylphosphonofluoridate (GF) (180)

CAS: *329-99-7*
Formula: *$C_7H_{14}FO_2P$*
Monoisotopic MW: *180.0715*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

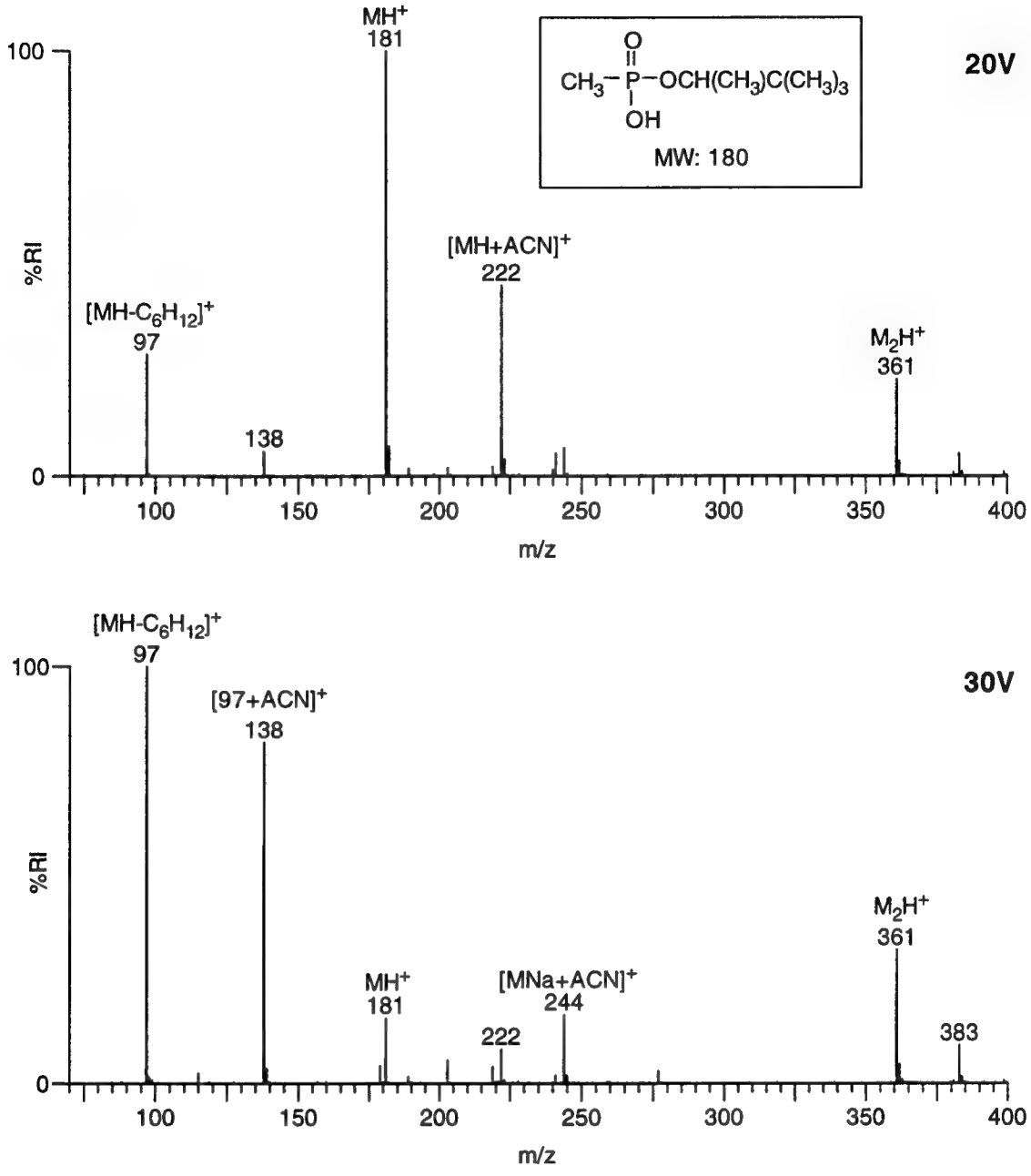


Figure 15. Pinacolyl methylphosphonic acid (180)

CAS: *616-52-4*
Formula: *$C_7H_{17}O_3P$*
Monoisotopic MW: *180.0915*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

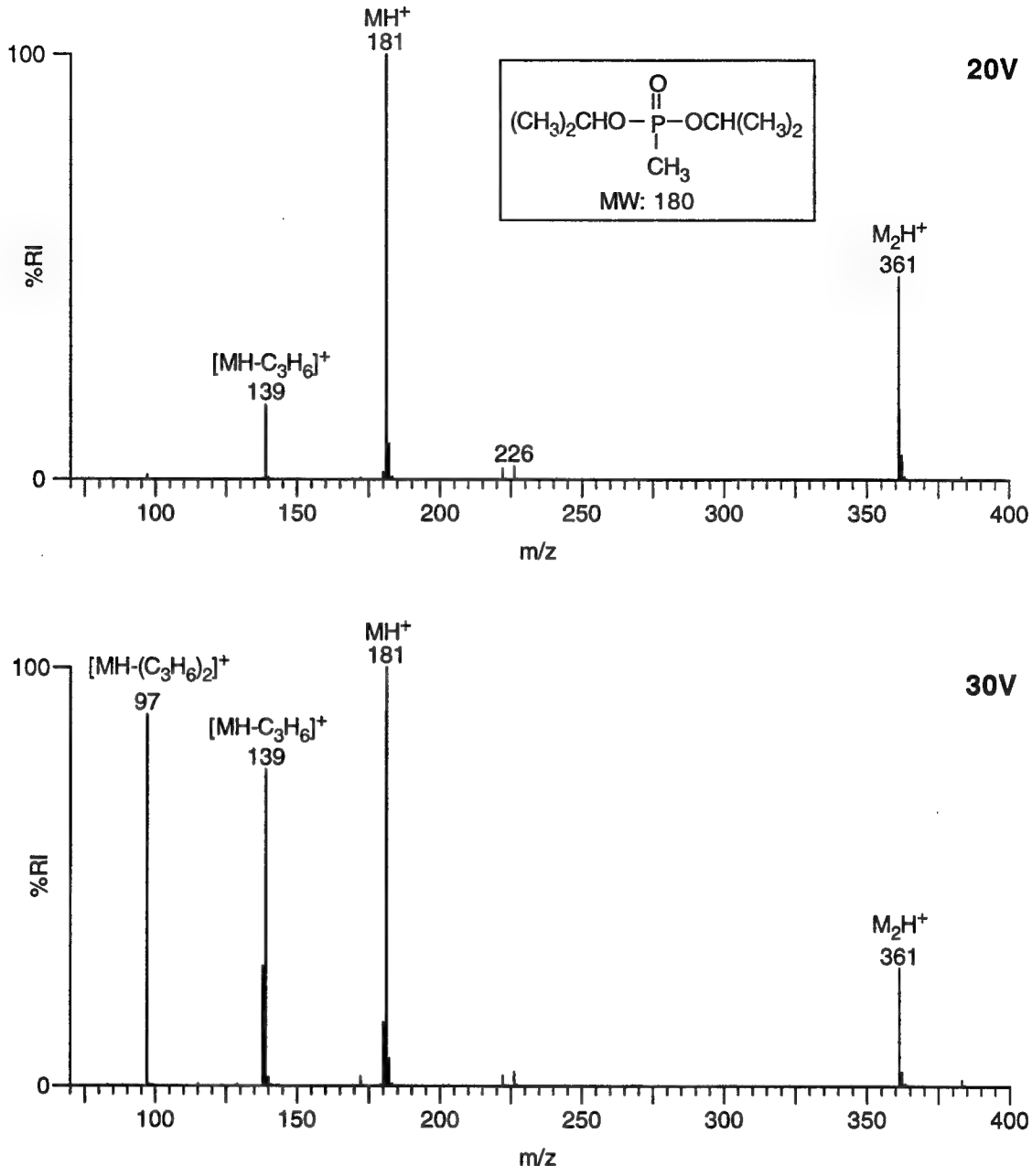


Figure 16. Diisopropyl methylphosphonate (180)

CAS: *1445-75-6*
Formula: *$C_7H_{17}O_3P$*
Monoisotopic MW: *180.0915*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

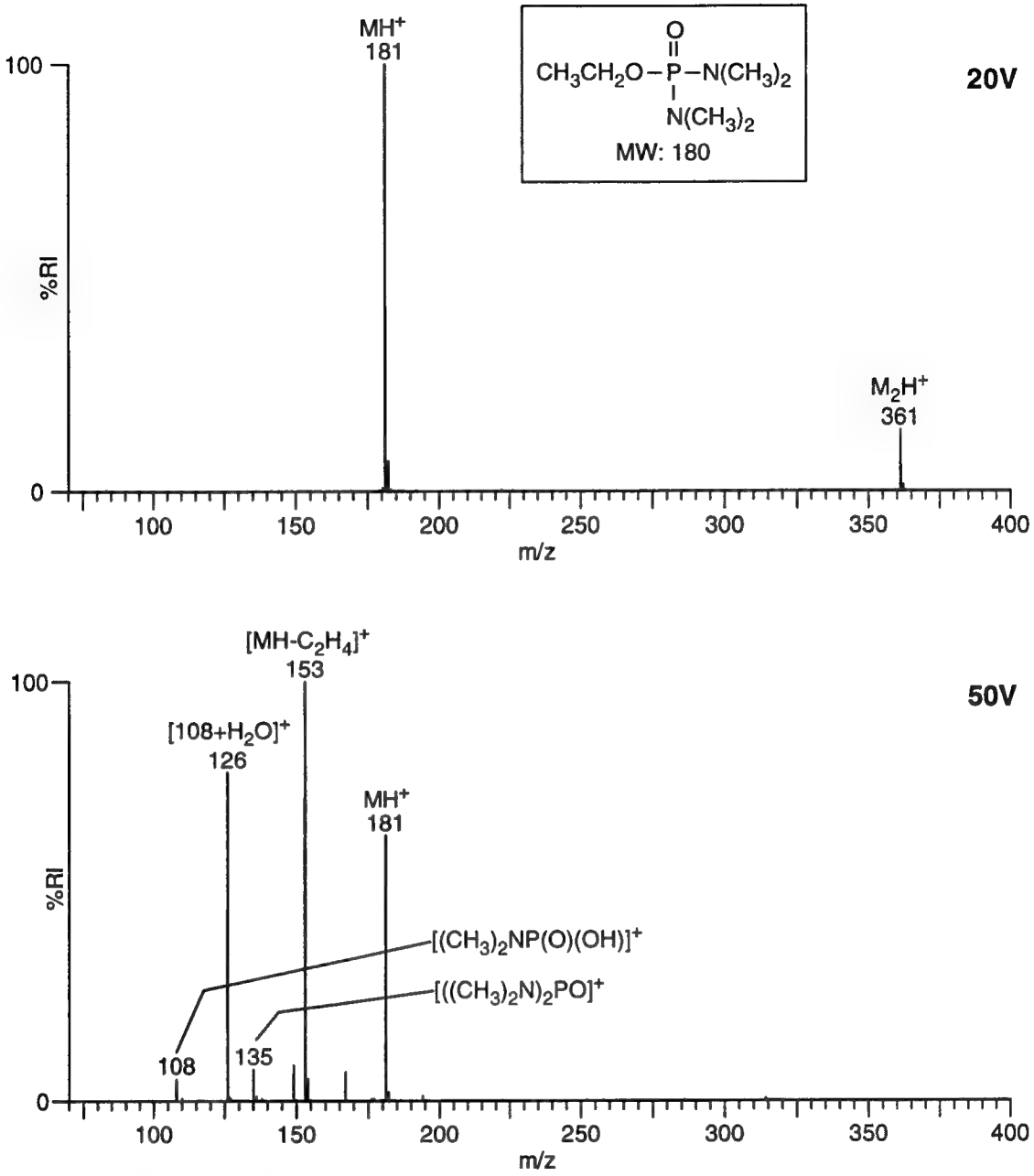


Figure 17. Ethyl tetramethylphosphorodiamidate (180)

CAS: *2404-65-1*
Formula: *$C_6H_{17}N_2O_2P$*
Monoisotopic MW: *180.1028*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

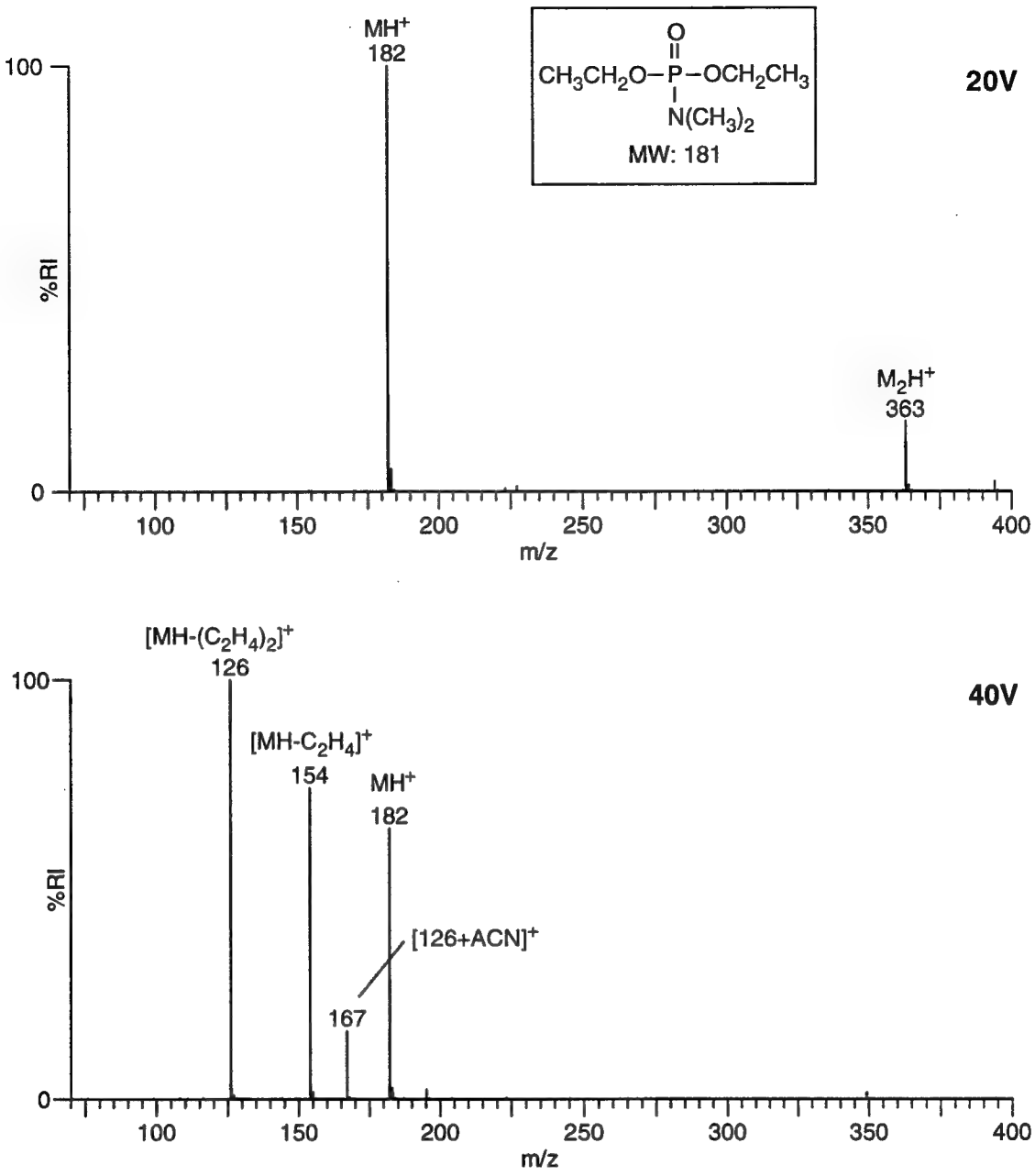


Figure 18. Diethyl dimethylphosphoramidate (181)

CAS: *2404-03-7*
Formula: *$C_6H_{16}NO_3P$*
Monoisotopic MW: *181.0868*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

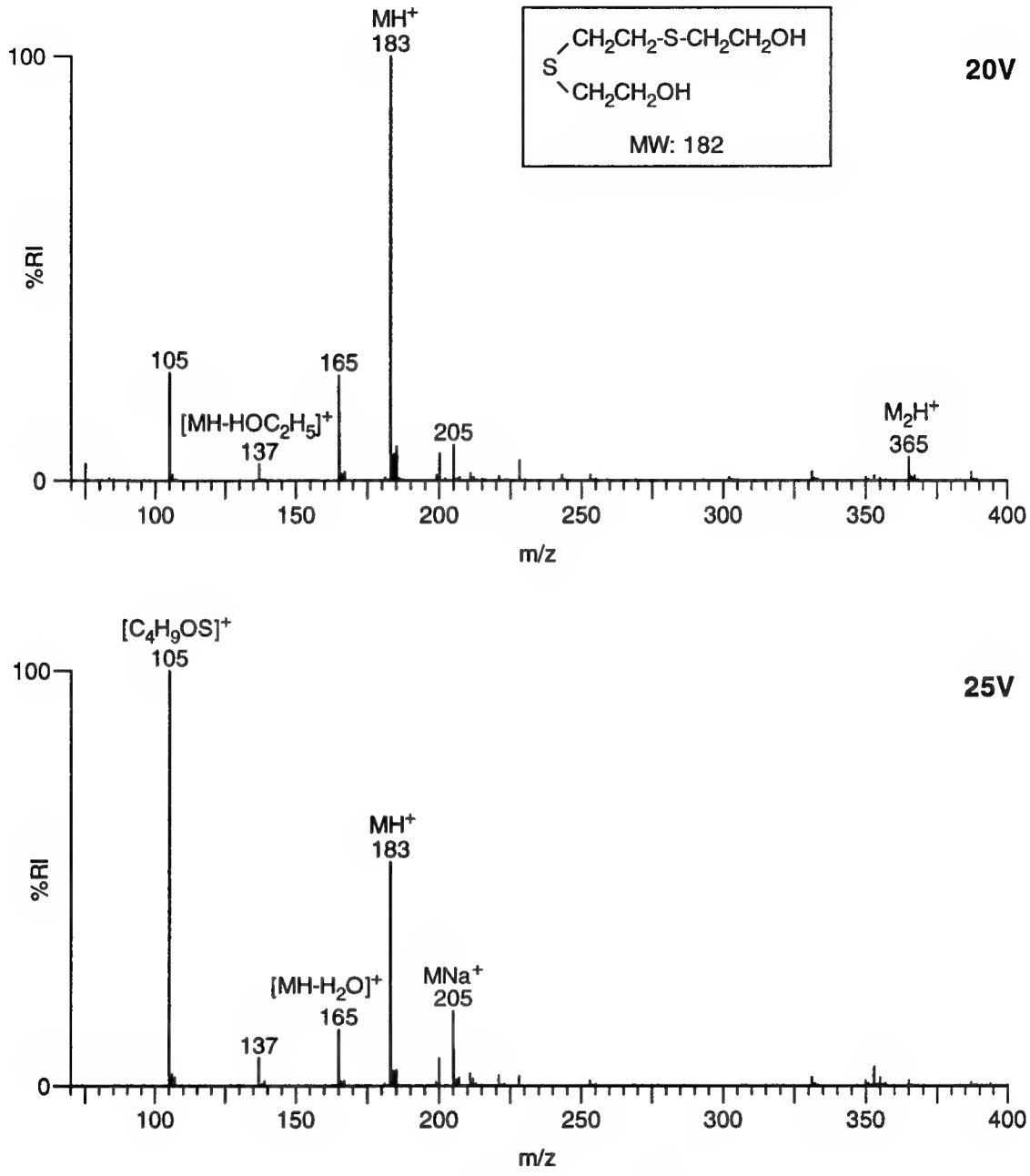


Figure 19. 3,6-Dithia-1,8-octanediol (182)

CAS: *5244-34-8*
Formula: *$C_6H_{14}O_2S_2$*
Monoisotopic MW: *182.0435*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

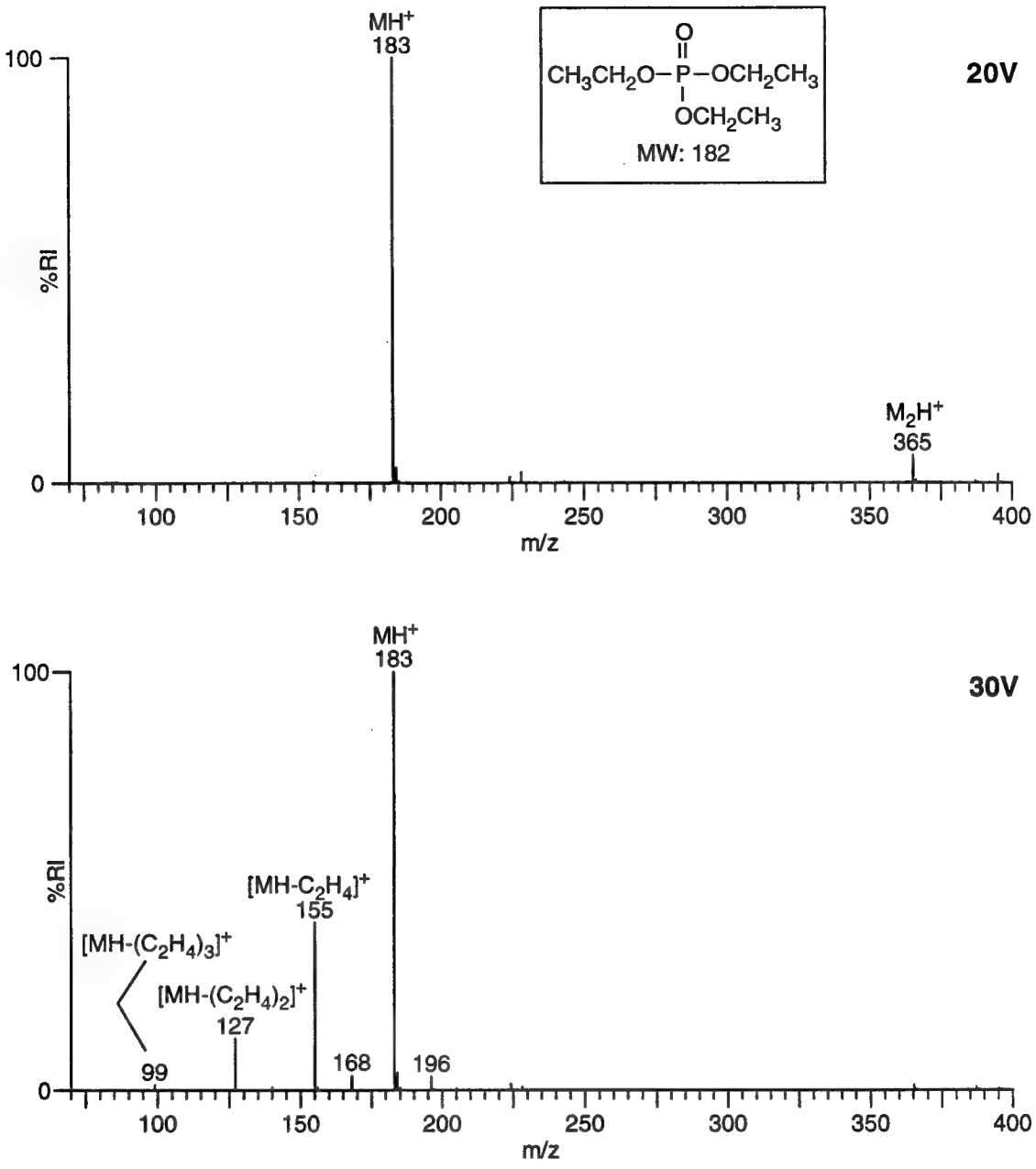


Figure 20. Triethyl phosphate (182)

CAS: *78-40-0*
Formula: *$C_6H_{15}O_4P$*
Monoisotopic MW: *182.0708*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

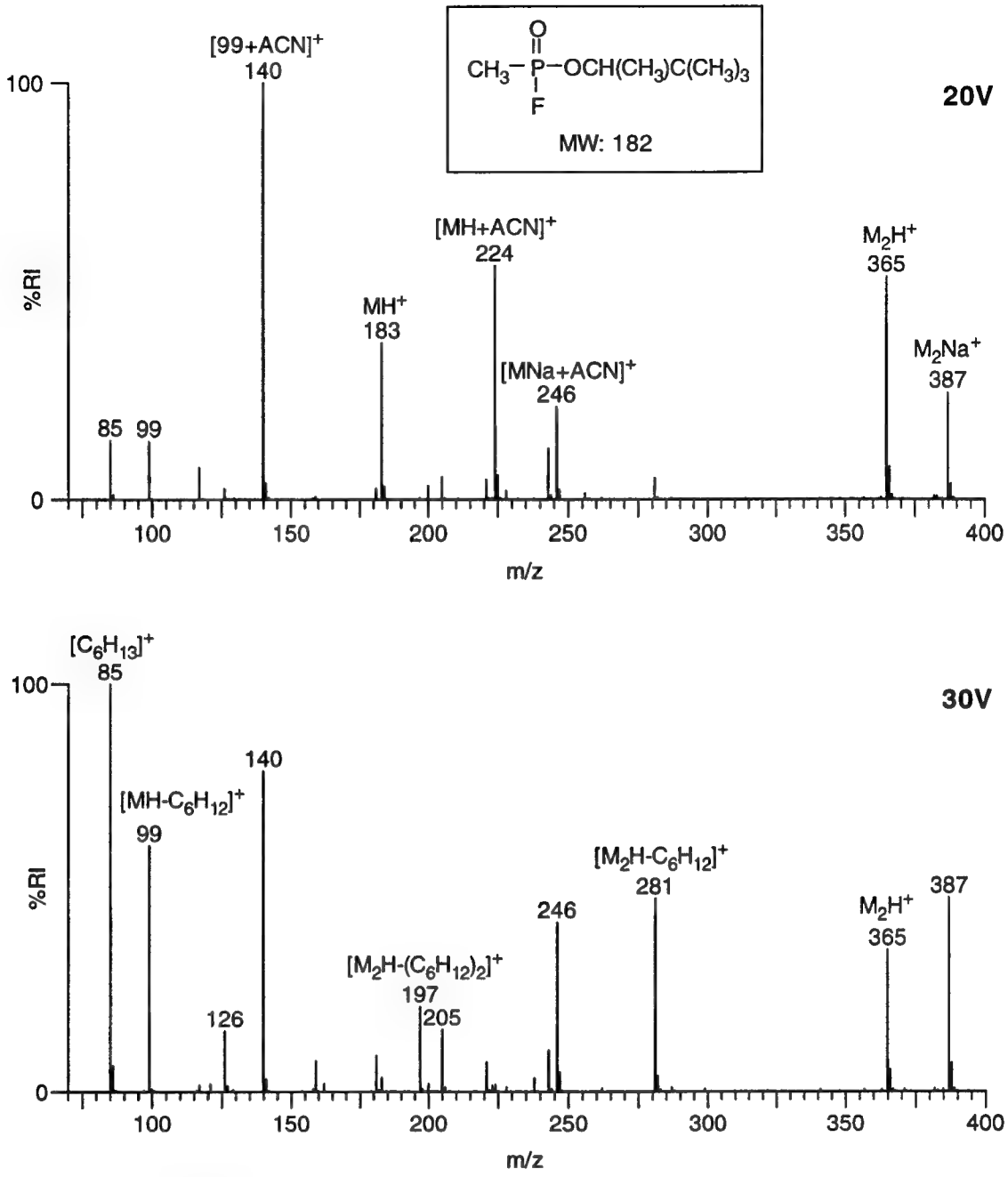


Figure 21. Pinacolyl methylphosphonofluoridate (Soman, GD) (182)

CAS: *96-64-0*
Formula: *$C_7H_{16}FO_2P$*
Monoisotopic MW: *182.0872*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

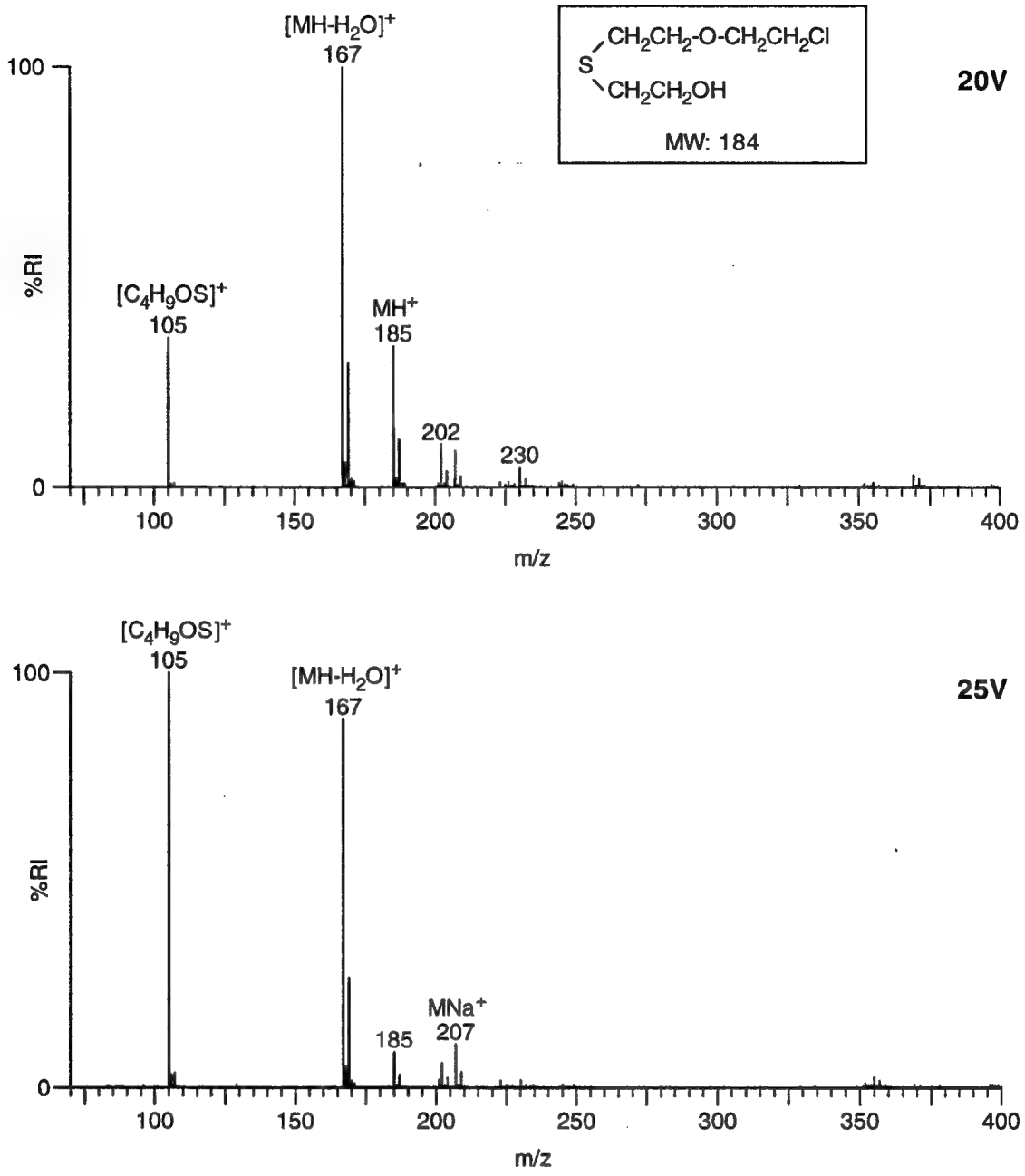


Figure 22. 8-Chloro-6-oxa-3-thia-1-octanol (184)

CAS: *Unknown*
Formula: *$C_6H_{13}ClO_2S$*
Monoisotopic MW: *184.0325*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

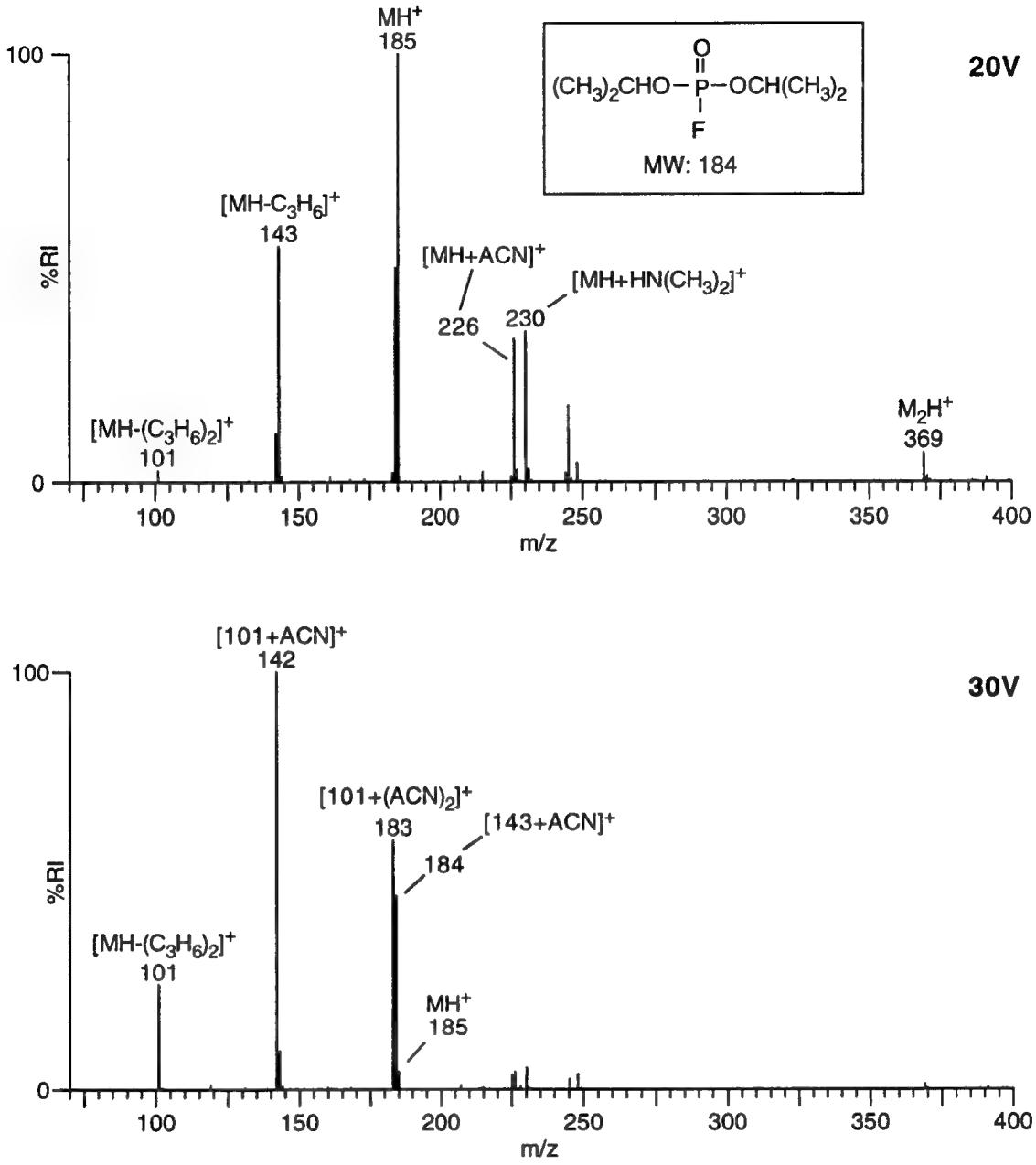


Figure 23. Diisopropyl phosphorofluoridate (DFP) (184)

CAS: *55-91-4*
Formula: *$C_6H_{14}FO_3P$*
Monoisotopic MW: *184.0665*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

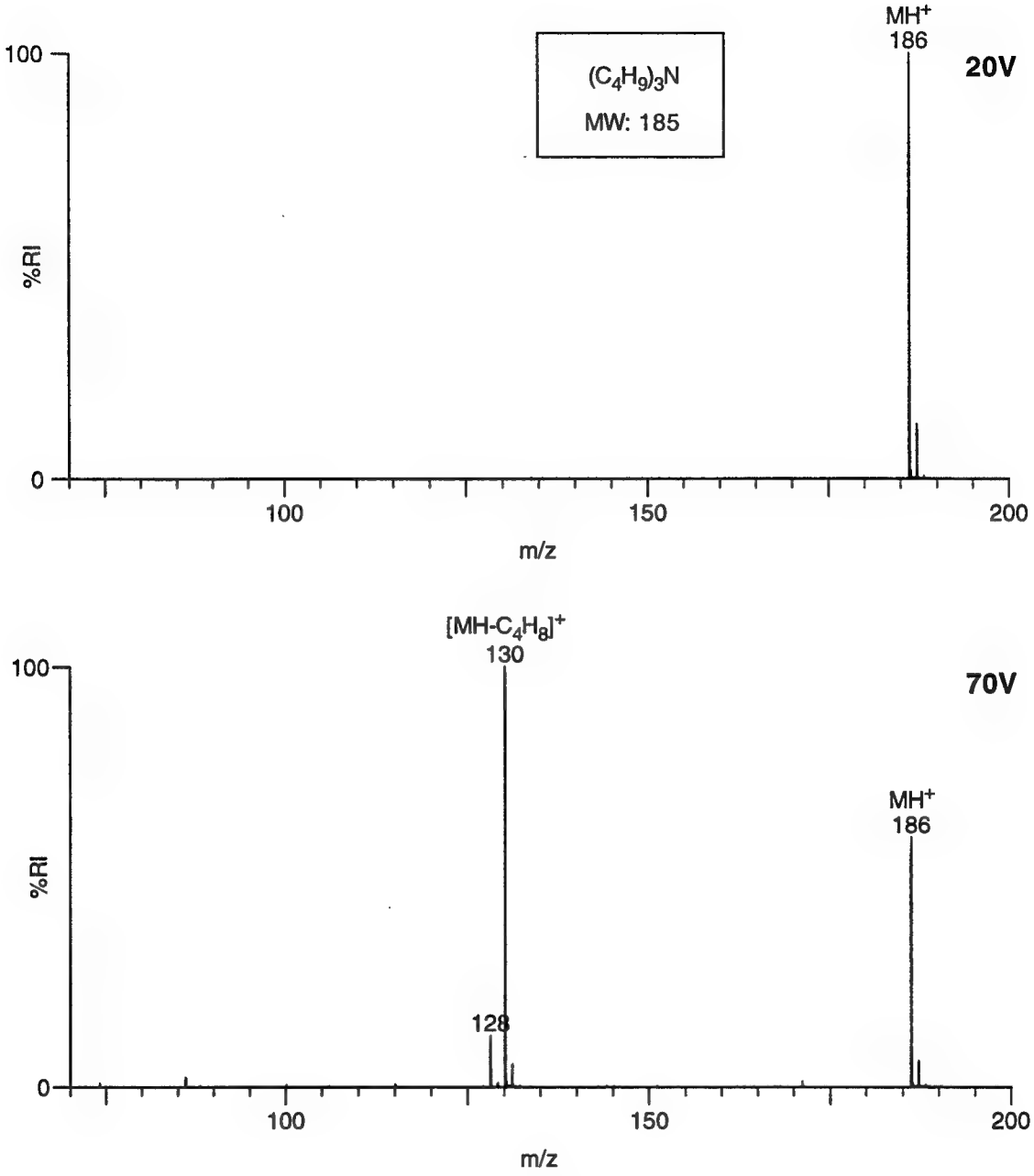


Figure 24. Tributylamine (185)

CAS: *102-82-9*
Formula: *$C_{12}H_{27}N$*
Monoisotopic MW: *185.2144*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

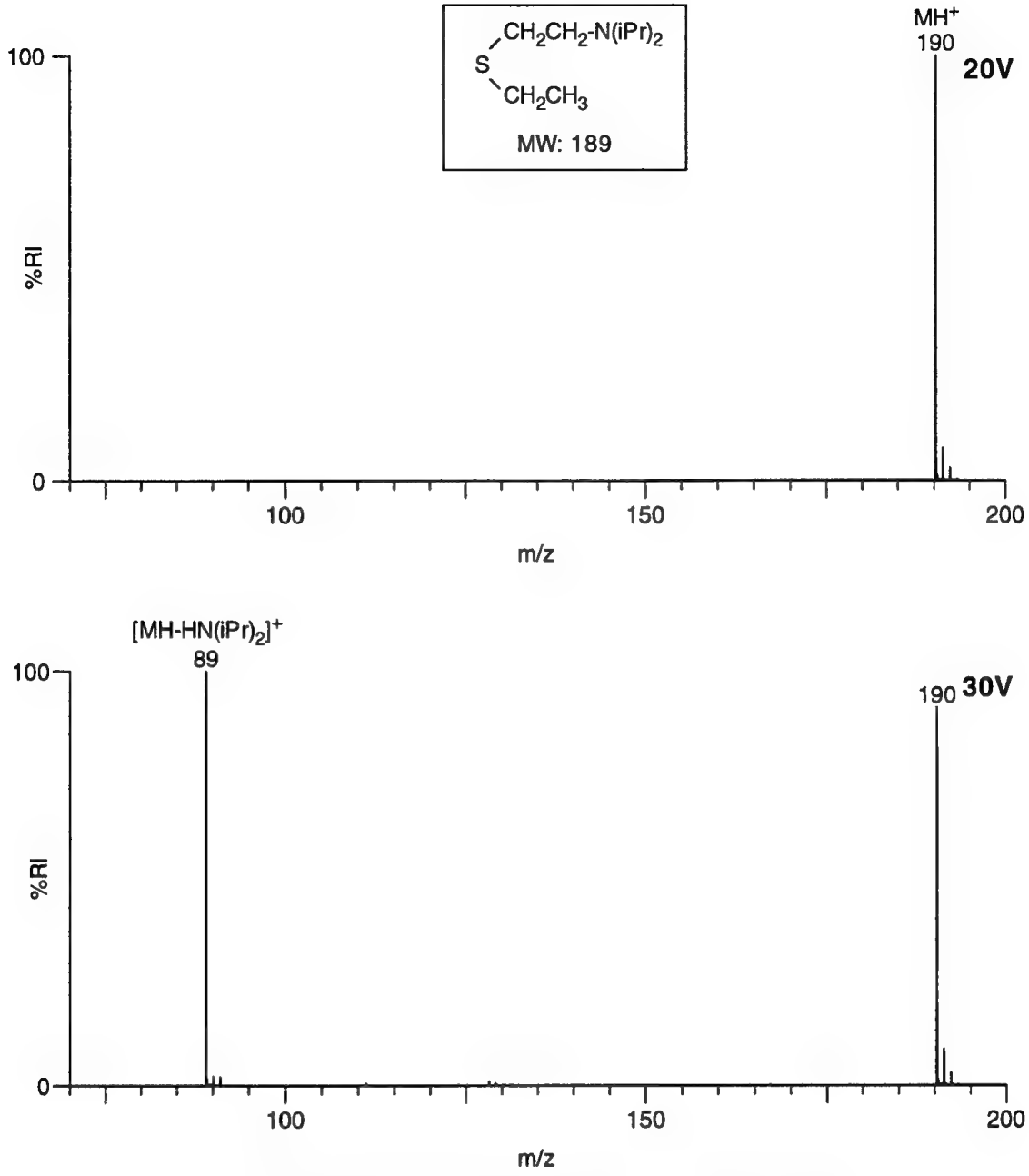


Figure 25. 2-(Diisopropylamino)ethyl ethyl sulfide (189)

CAS:
Formula: $C_{10}H_{23}NS$
Monoisotopic MW: *189.1551*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

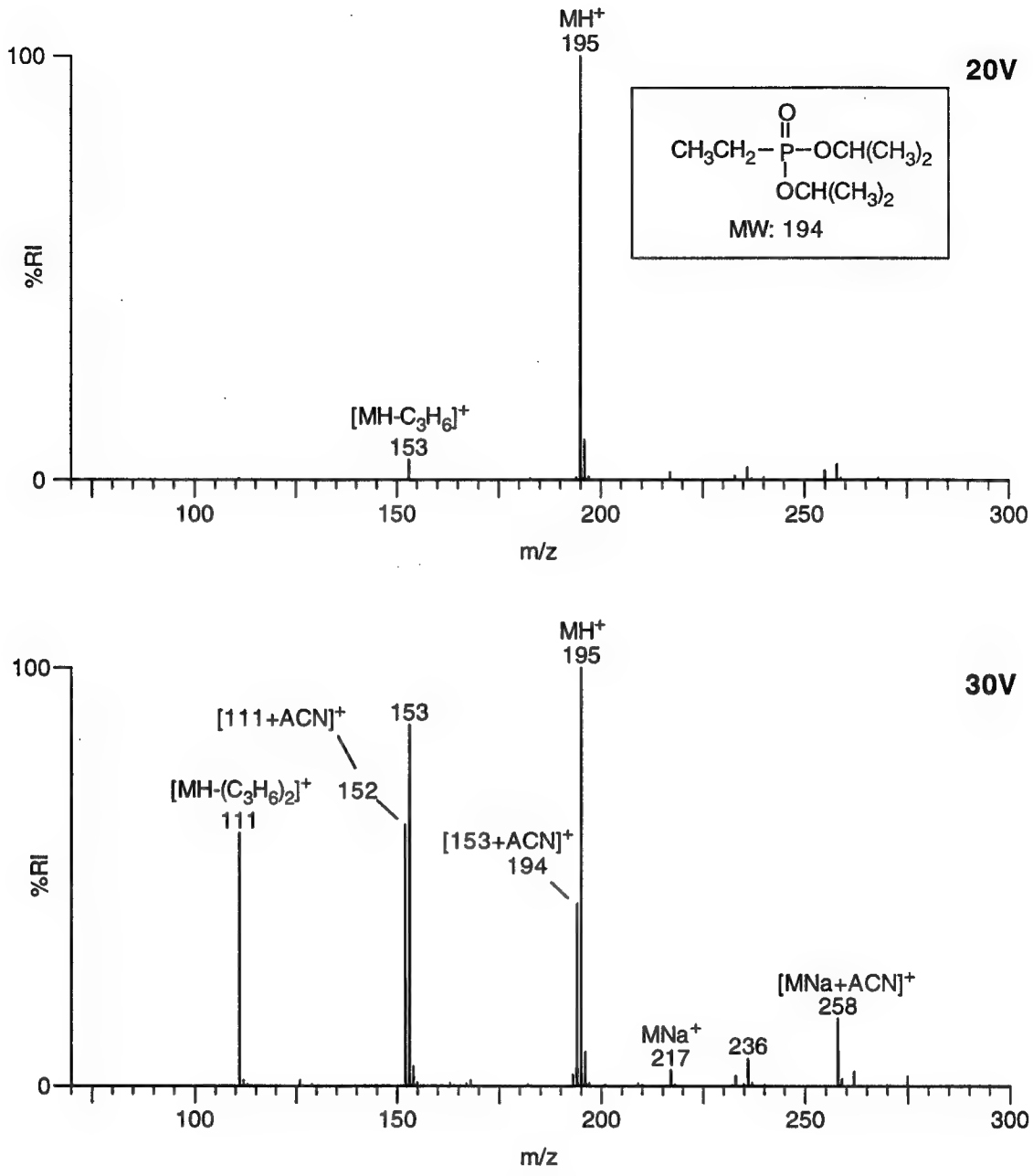


Figure 26. Diisopropyl ethylphosphonate (194)

CAS: *1067-69-2*
Formula: *$C_8H_{19}O_3P$*
Monoisotopic MW: *194.1072*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

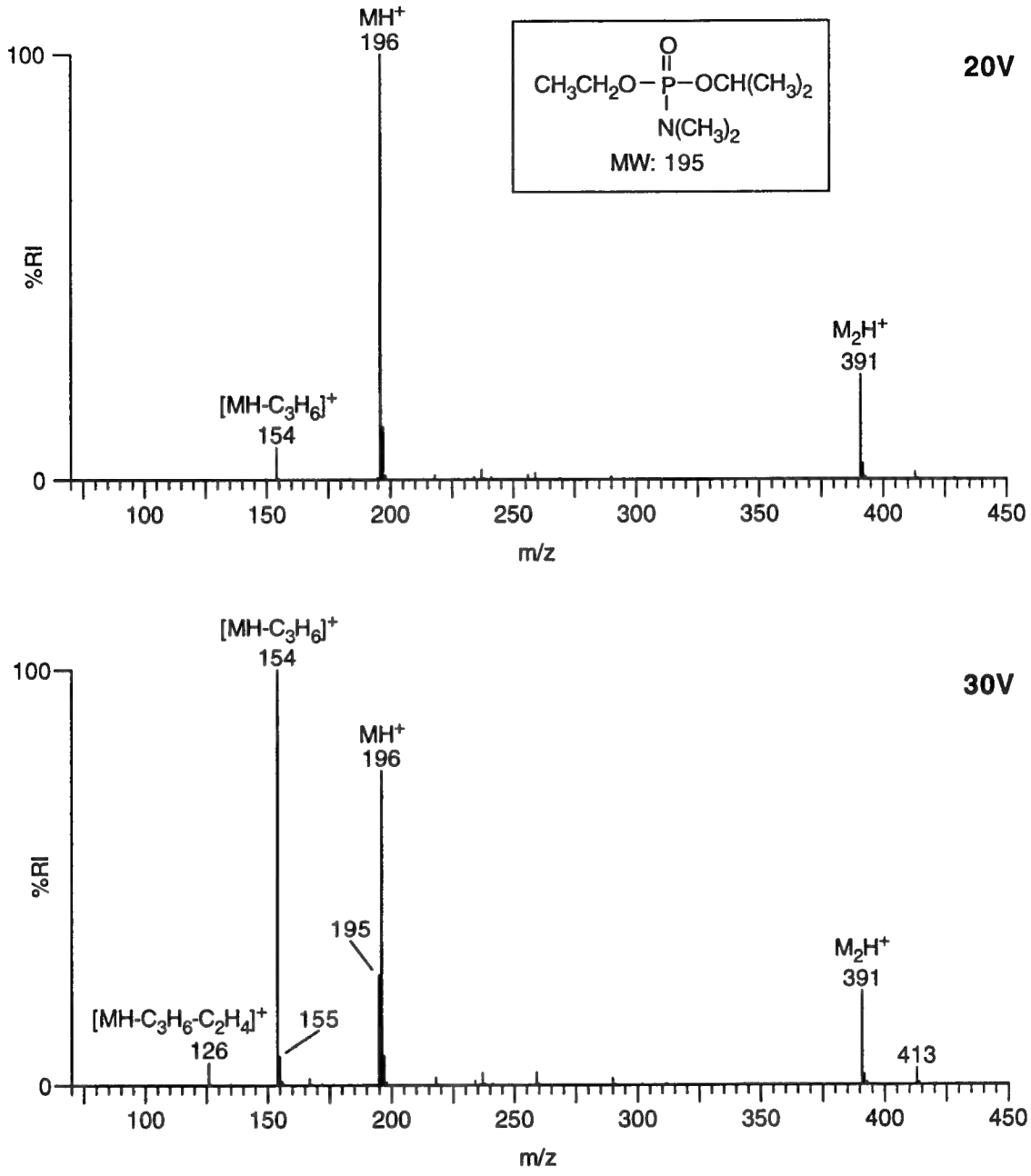


Figure 27. Ethyl isopropyl dimethylphosphoramidate (195)

CAS: *99520-56-6*
Formula: *$C_7H_{18}NO_3P$*
Monoisotopic MW: *195.1024*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

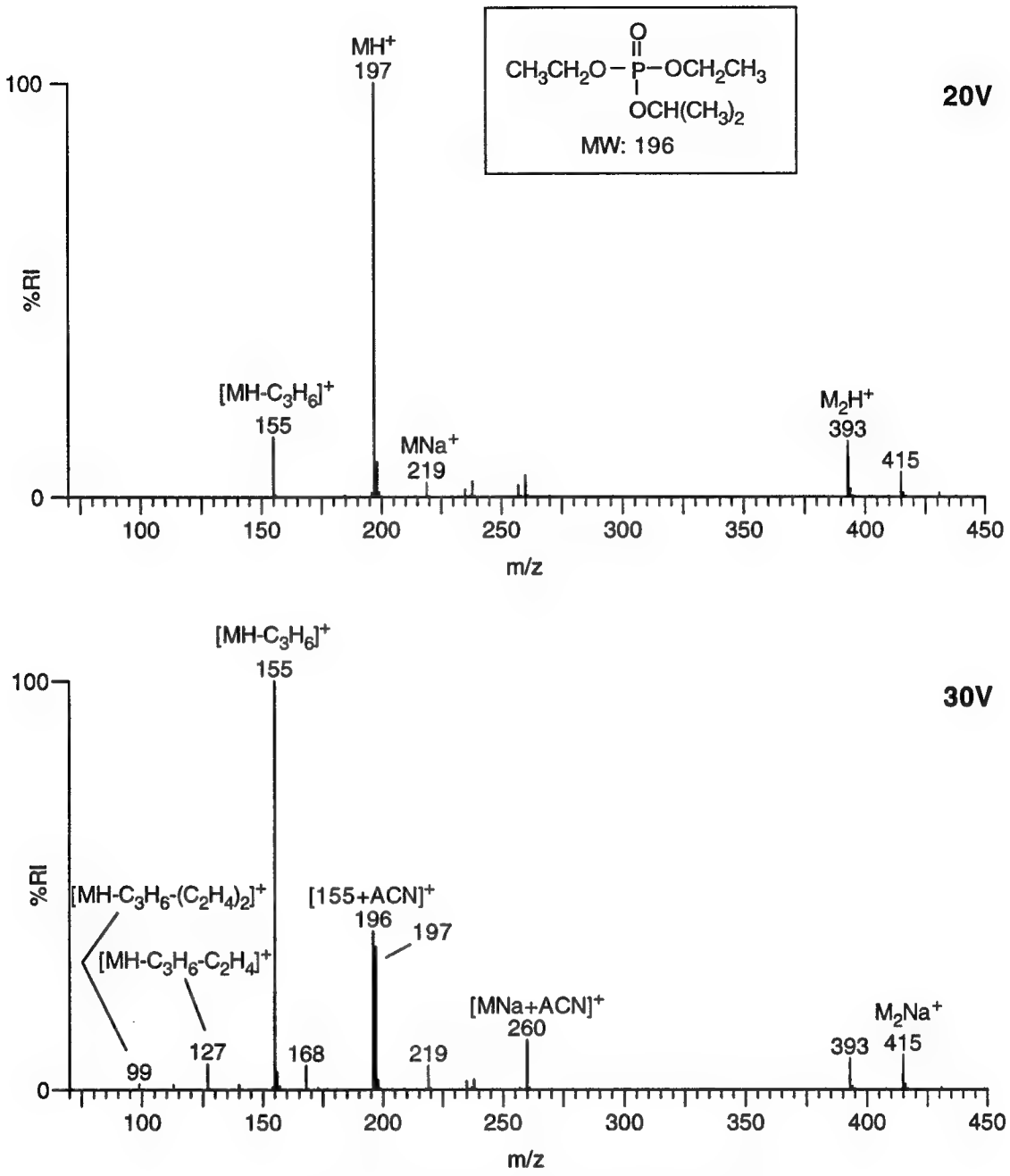


Figure 28. Diethyl isopropyl phosphate (196)

CAS: *2736-99-4*
Formula: *$C_7H_{17}O_4P$*
Monoisotopic MW: *196.0864*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

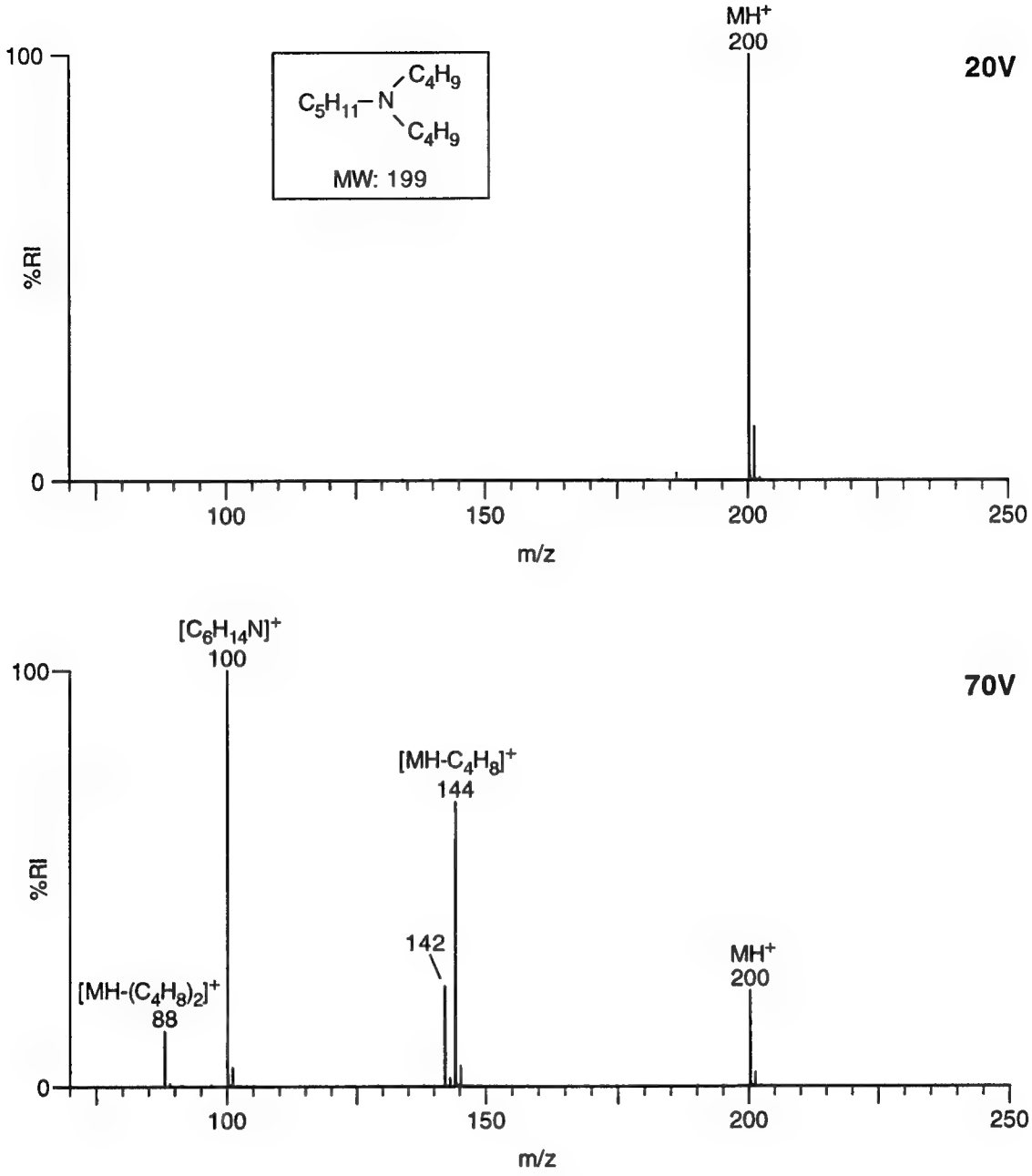


Figure 29. Pentyl dibutylamine (199)

CAS: *6703-22-6*
Formula: *$C_{13}H_{29}N$*
Monoisotopic MW: *199.2300*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

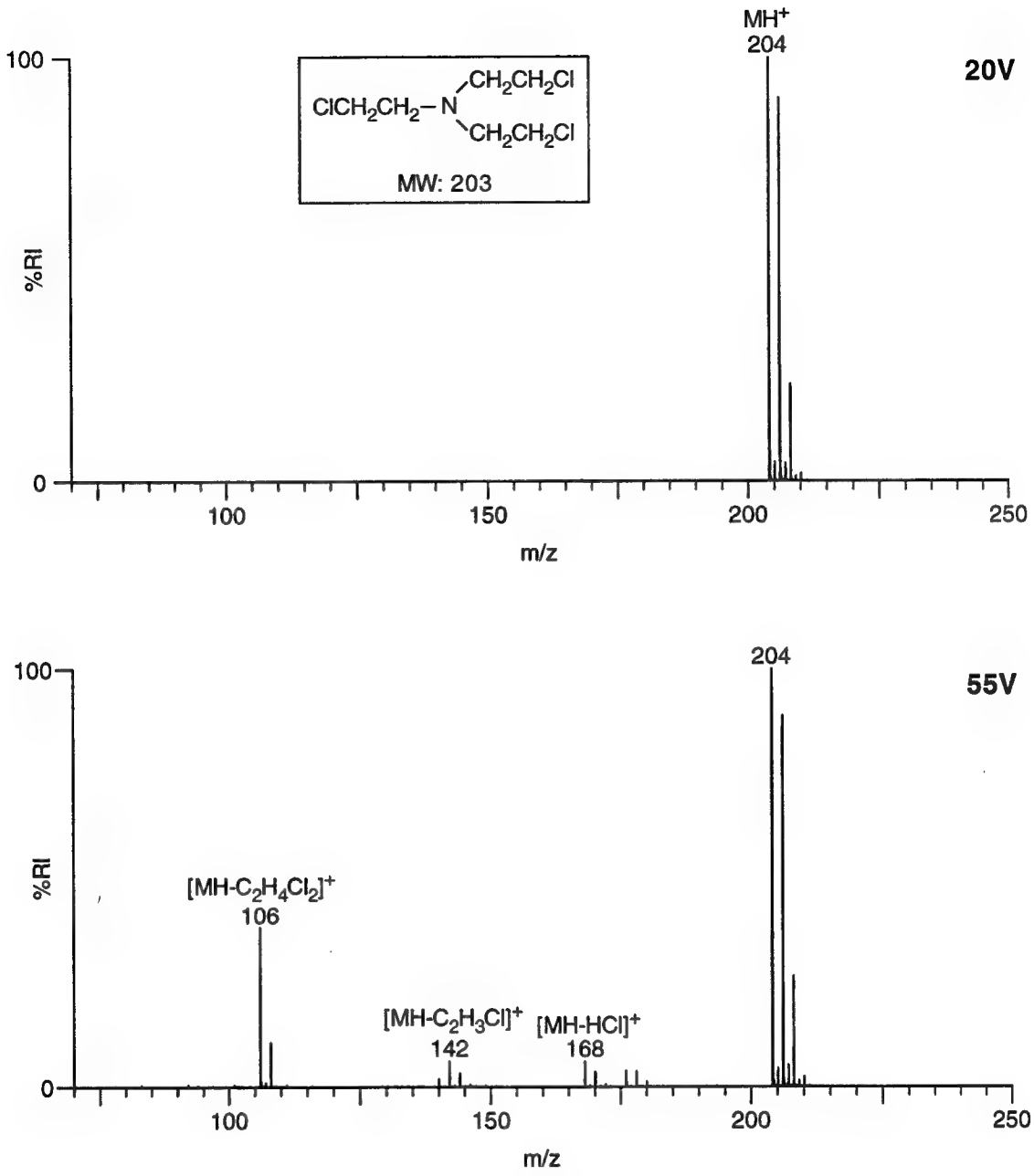


Figure 30. 2,2',2''-Trichlorotriethylamine (HN3) (203)

CAS: *555-77-1*
Formula: *$C_6H_{12}Cl_3N$*
Monoisotopic MW: *203.0035*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

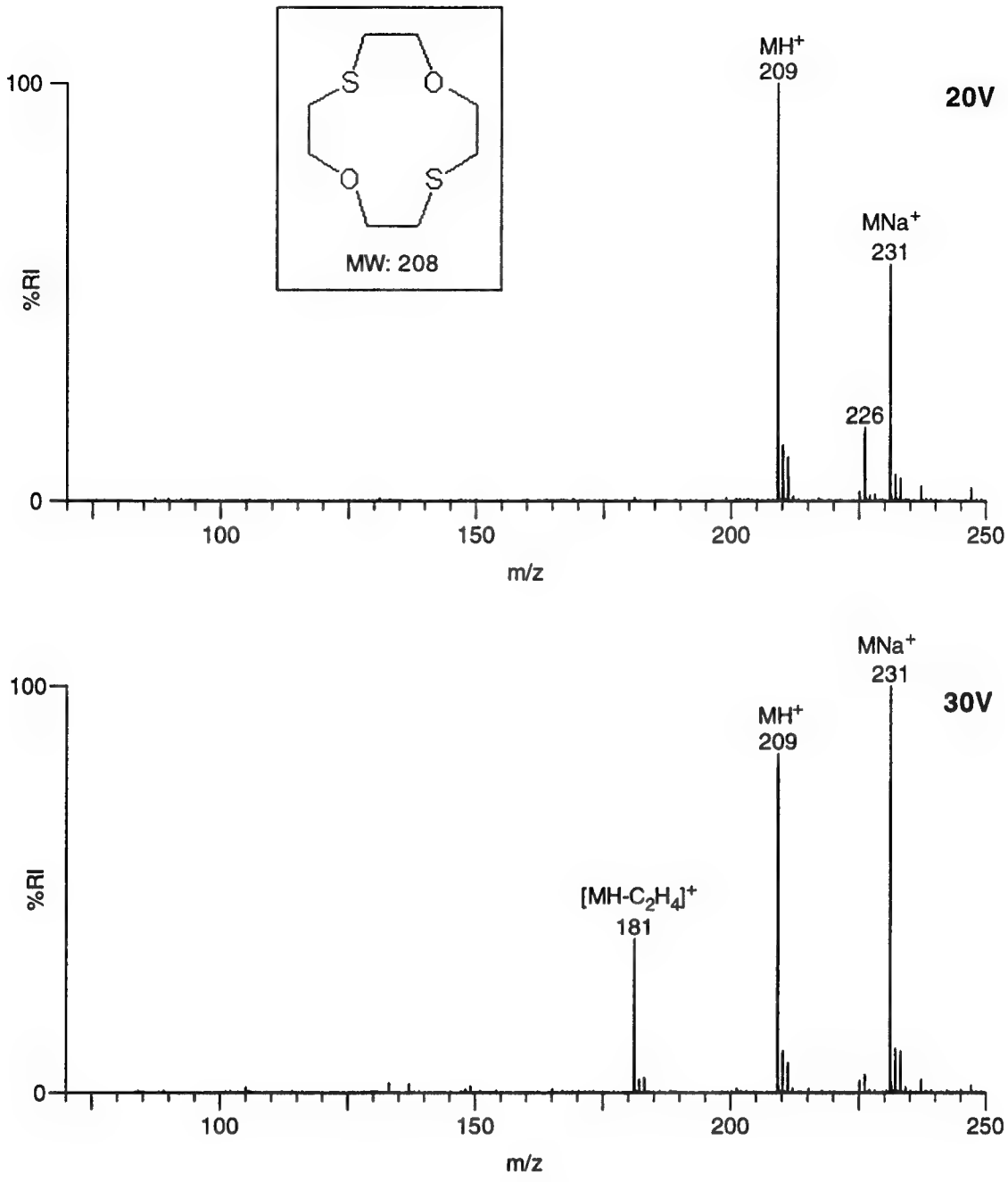


Figure 31. 1,7-Dioxa-4,10-dithiacyclodecane (208)

CAS: *294-95-1*
Formula: *$C_8H_{16}O_2S_2$*
Monoisotopic MW: *208.0592*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

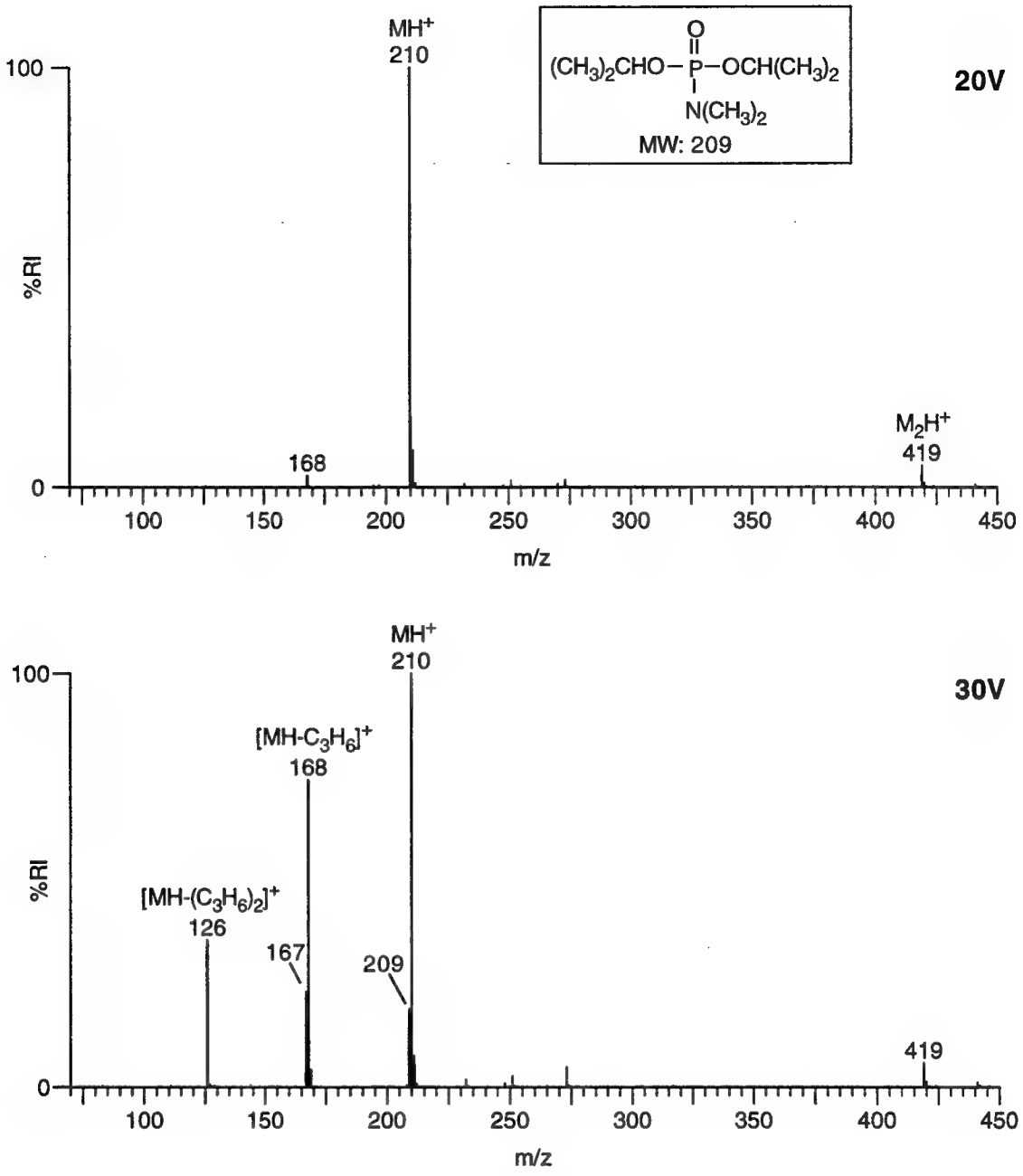


Figure 32. Diisopropyl dimethylphosphoramidate (209)

CAS: *2404-04-8*
Formula: *$C_8H_{20}NO_3P$*
Monoisotopic MW: *209.1181*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

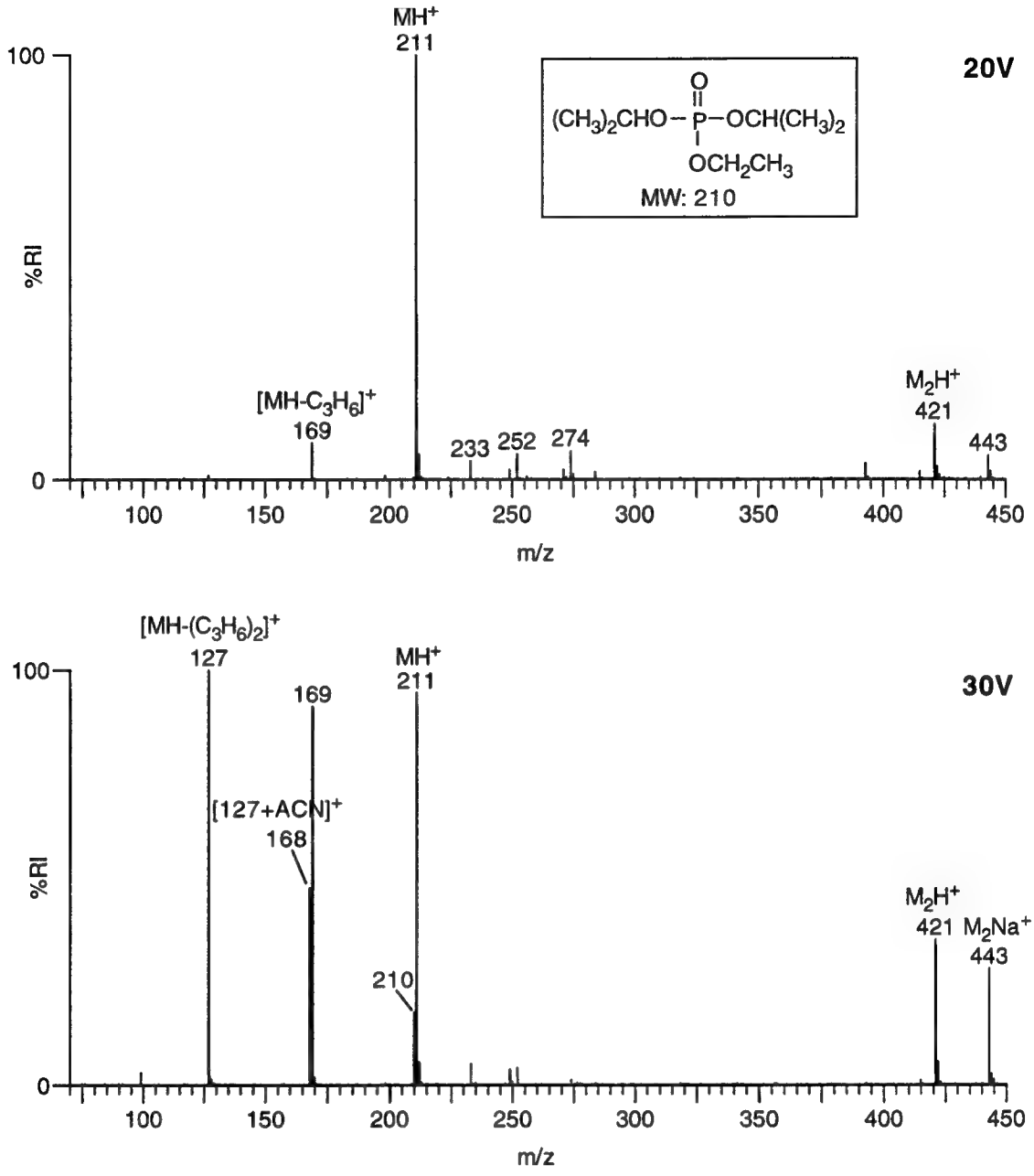


Figure 33. Diisopropyl ethyl phosphate (210)

CAS: *2695-64-6*
Formula: *$C_8H_{19}O_4P$*
Monoisotopic MW: *210.1021*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

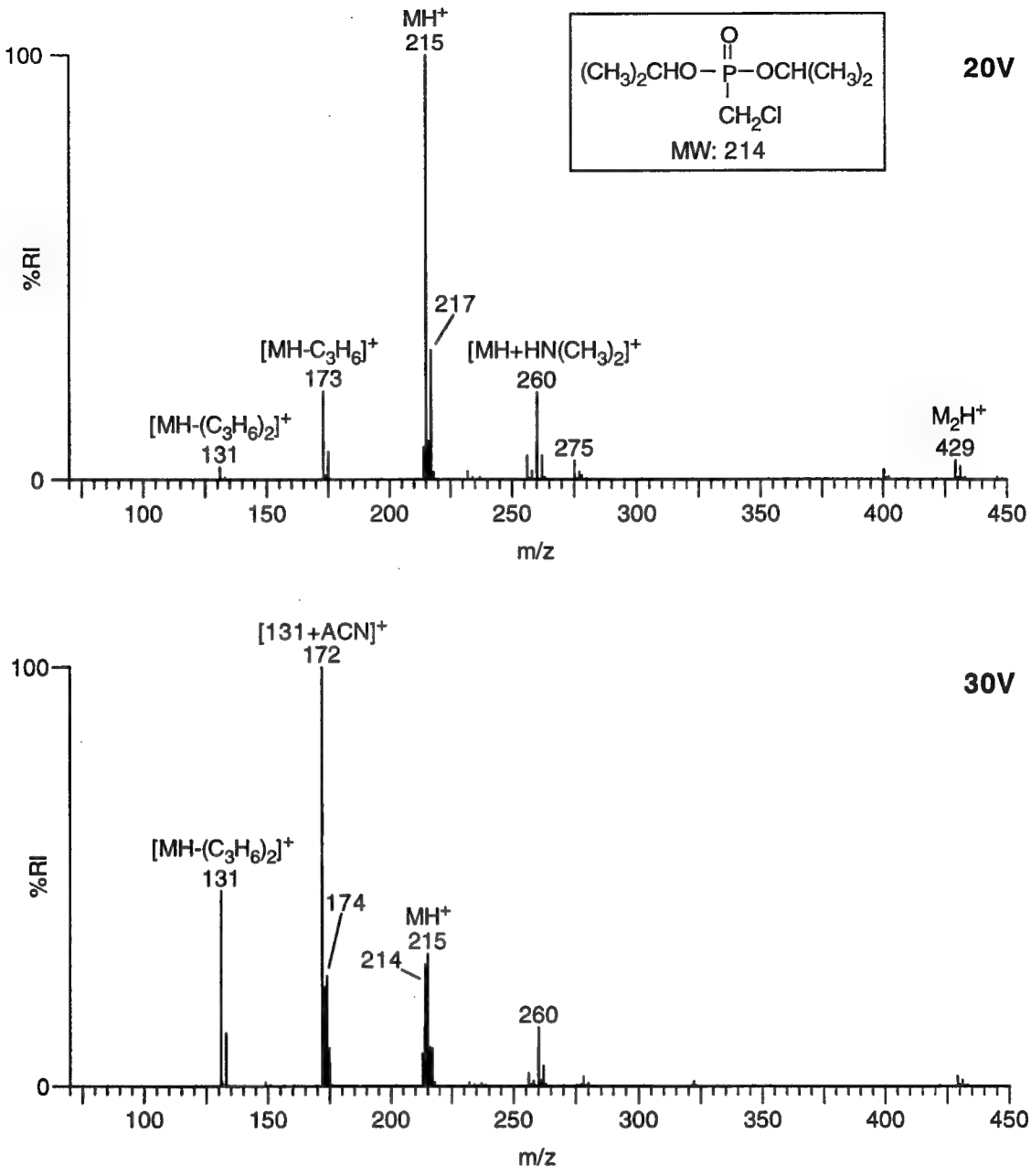


Figure 34. Diisopropyl chloromethylphosphonate (214)

CAS: *6954-83-2*
Formula: *$C_7H_{16}ClO_3P$*
Monoisotopic MW: *214.0526*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

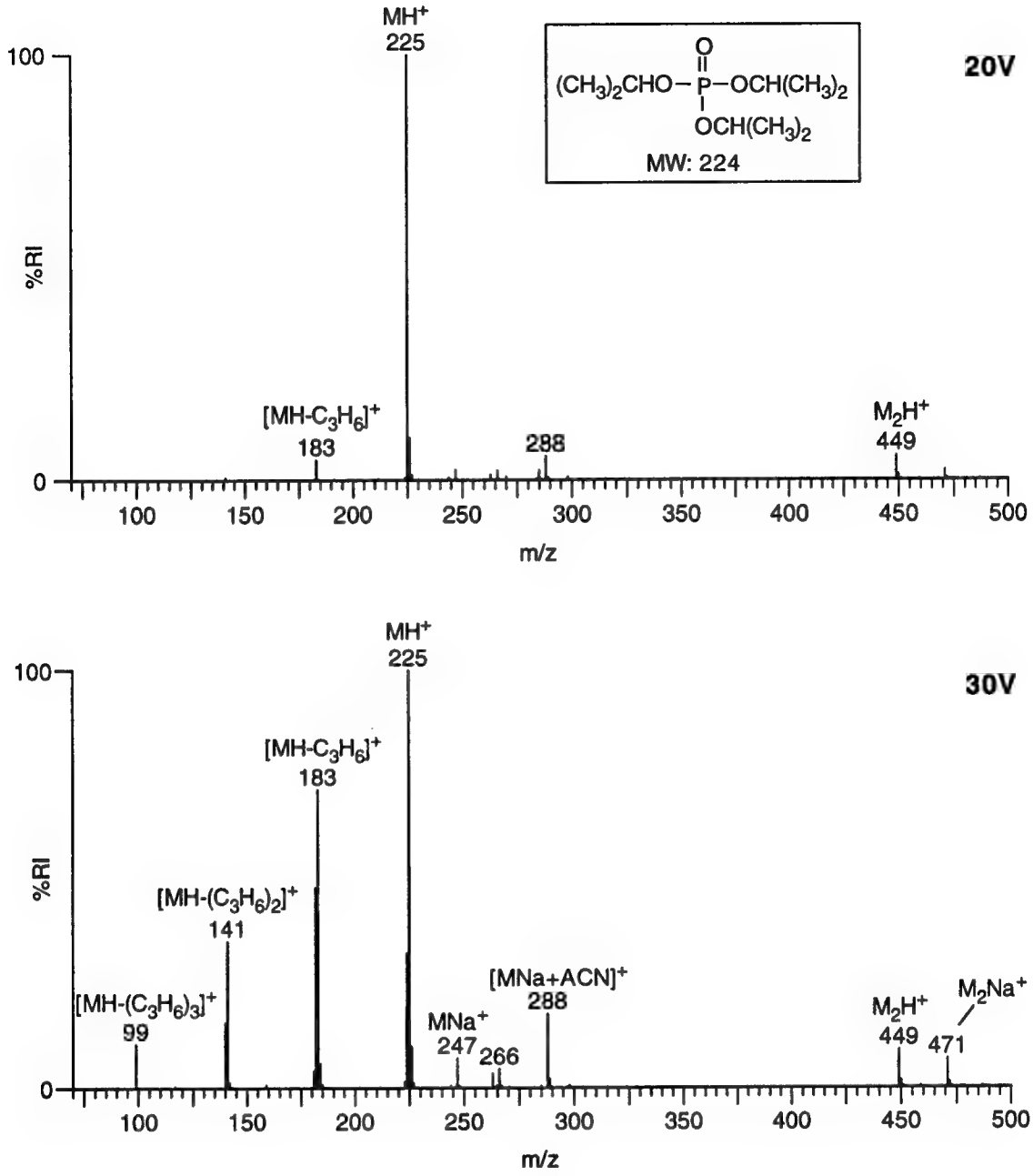


Figure 35. Triisopropyl phosphate (224)

CAS: *513-08-6*
Formula: *$C_9H_{21}O_4P$*
Monoisotopic MW: *224.1177*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

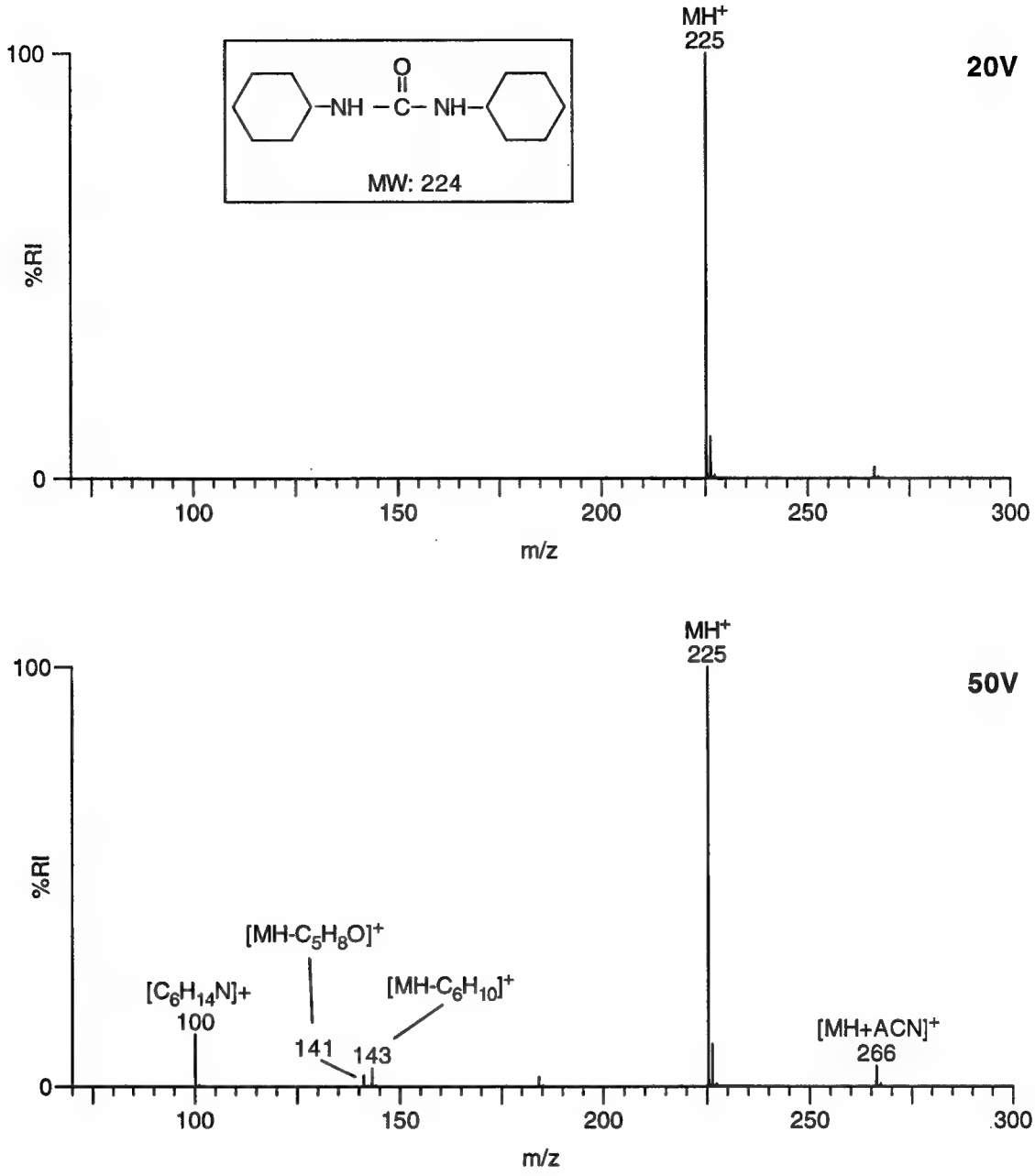


Figure 36. N,N'-Dicyclohexylurea (224)

CAS: *2387-23-7*
Formula: *$C_{13}H_{24}N_2O$*
Monoisotopic MW: *224.1889*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

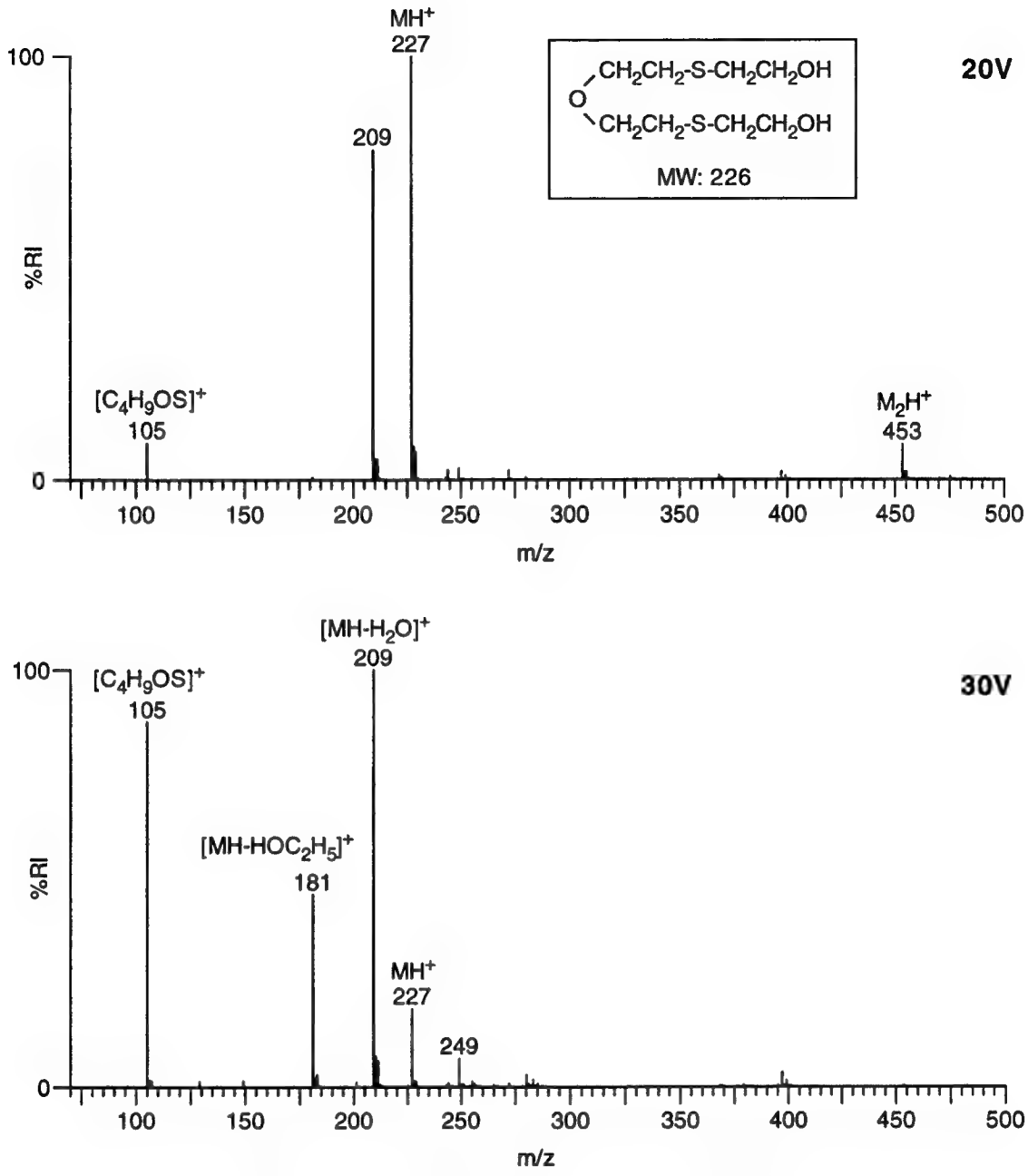


Figure 37. 6-Oxa-3,9-dithia-1,11-undecanediol (226)

CAS: *7426-02-0*
Formula: *$C_8H_{18}O_3S_2$*
Monoisotopic MW: *226.0697*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

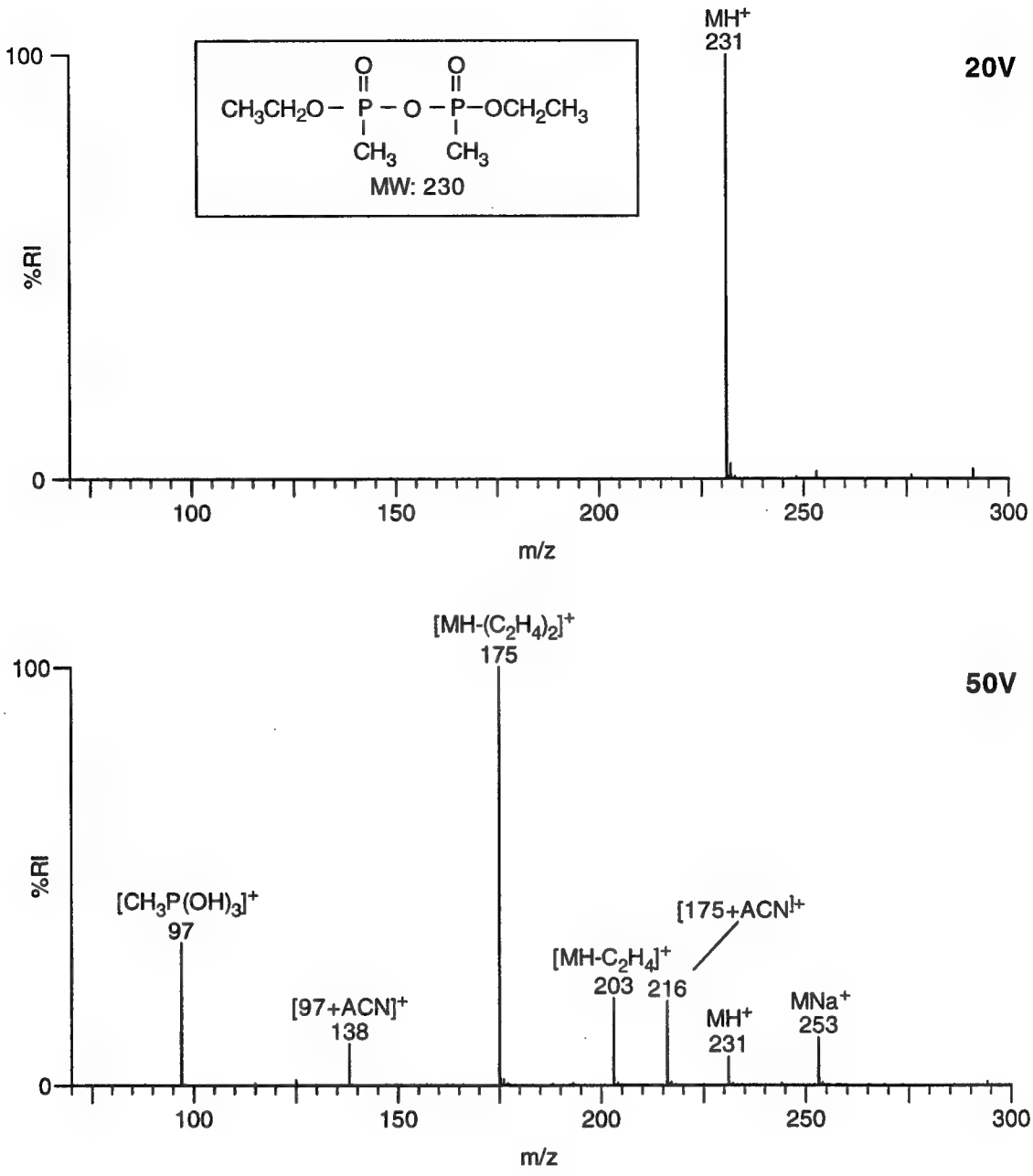


Figure 38. Diethyl dimethylpyrophosphonate (230)

CAS: *32288-17-8*
Formula: *$C_6H_{16}O_5P_2$*
Monoisotopic MW: *230.0473*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

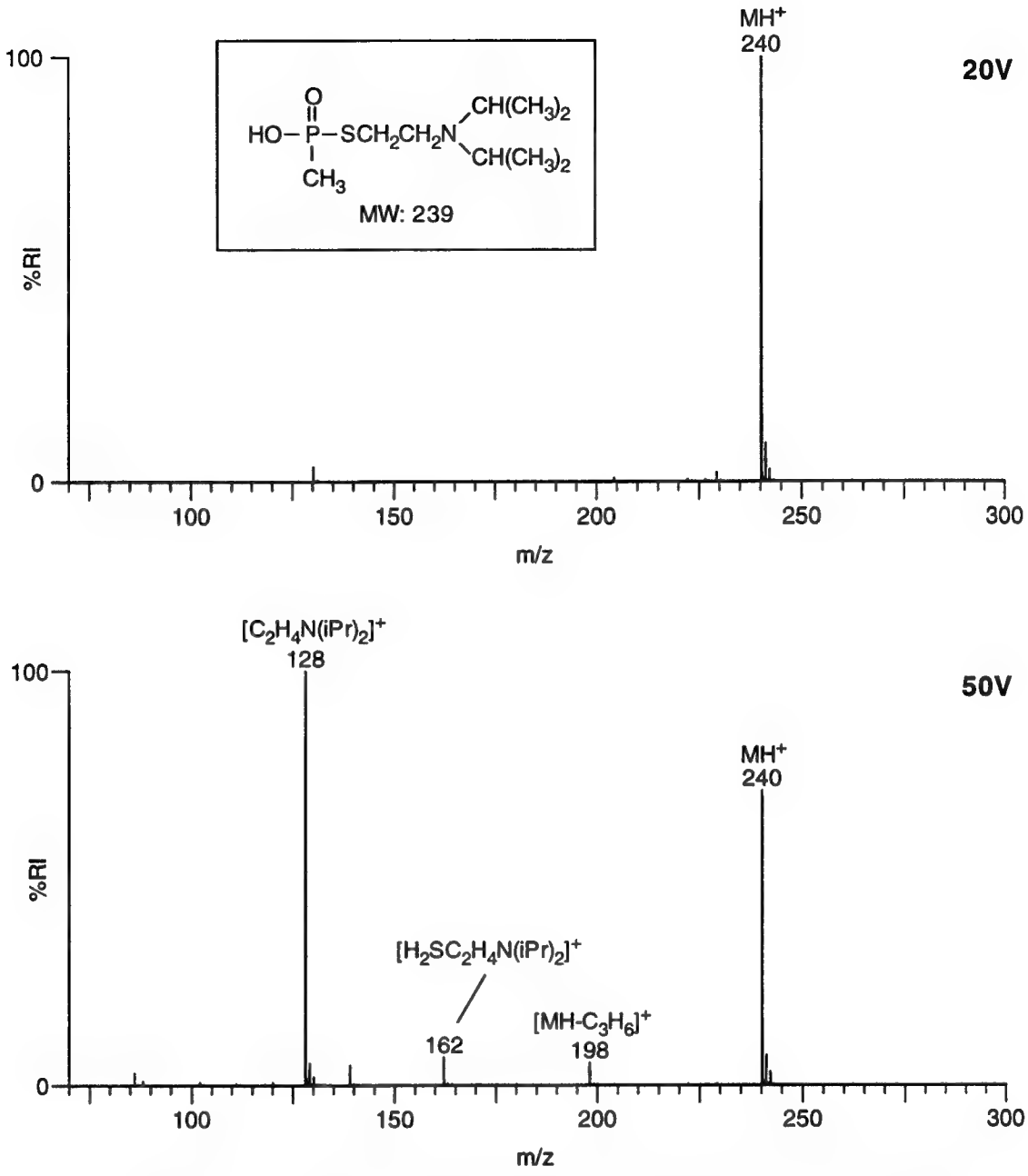


Figure 39. S-[2-(Diisopropylamino) ethyl]methylphosphonothiolate (239)

CAS: *73207-98-4*
Formula: *$C_9H_{22}NO_2PS$*
Monoisotopic MW: *239.1109*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

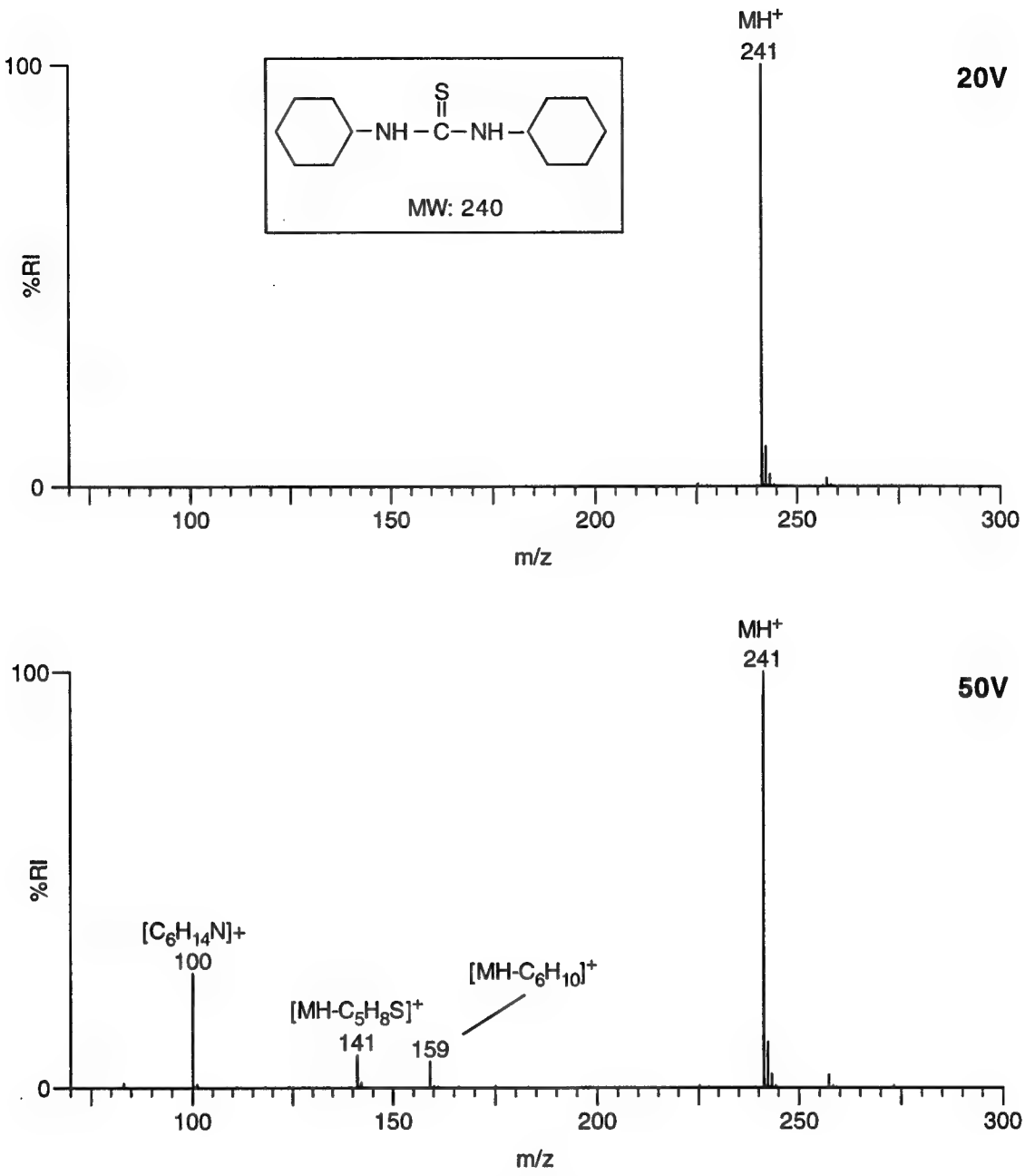


Figure 40. N,N'-Dicyclohexylthiourea (240)

CAS: *1212-29-9*
Formula: *$C_{13}H_{24}N_2S$*
Monoisotopic MW: *240.1660*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

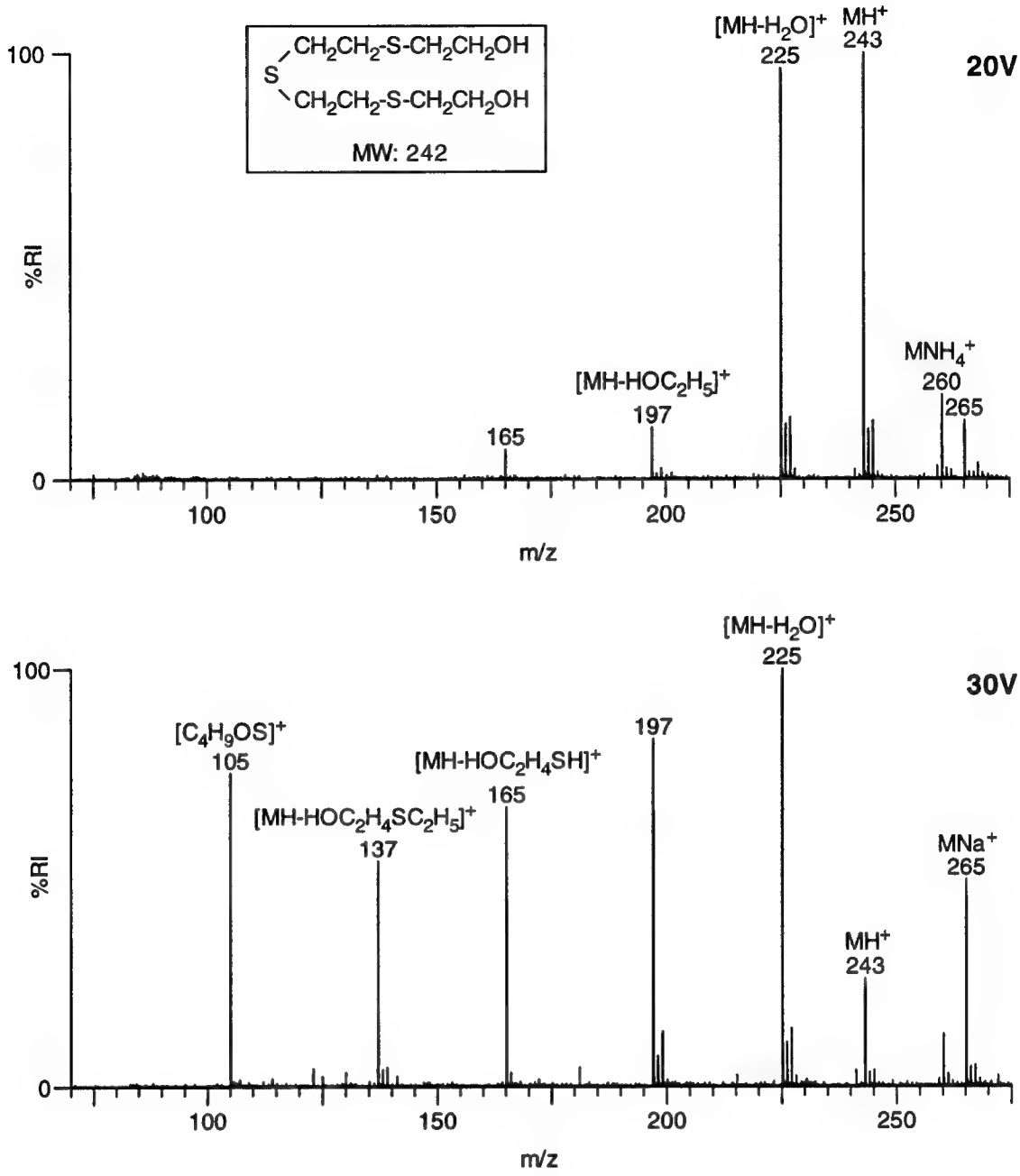


Figure 41. 3,6,9-Trithia-1,11-undecanediol (242)

CAS: *14440-77-8*
Formula: *$C_8H_{18}O_2S_3$*
Monoisotopic MW: *242.0469*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

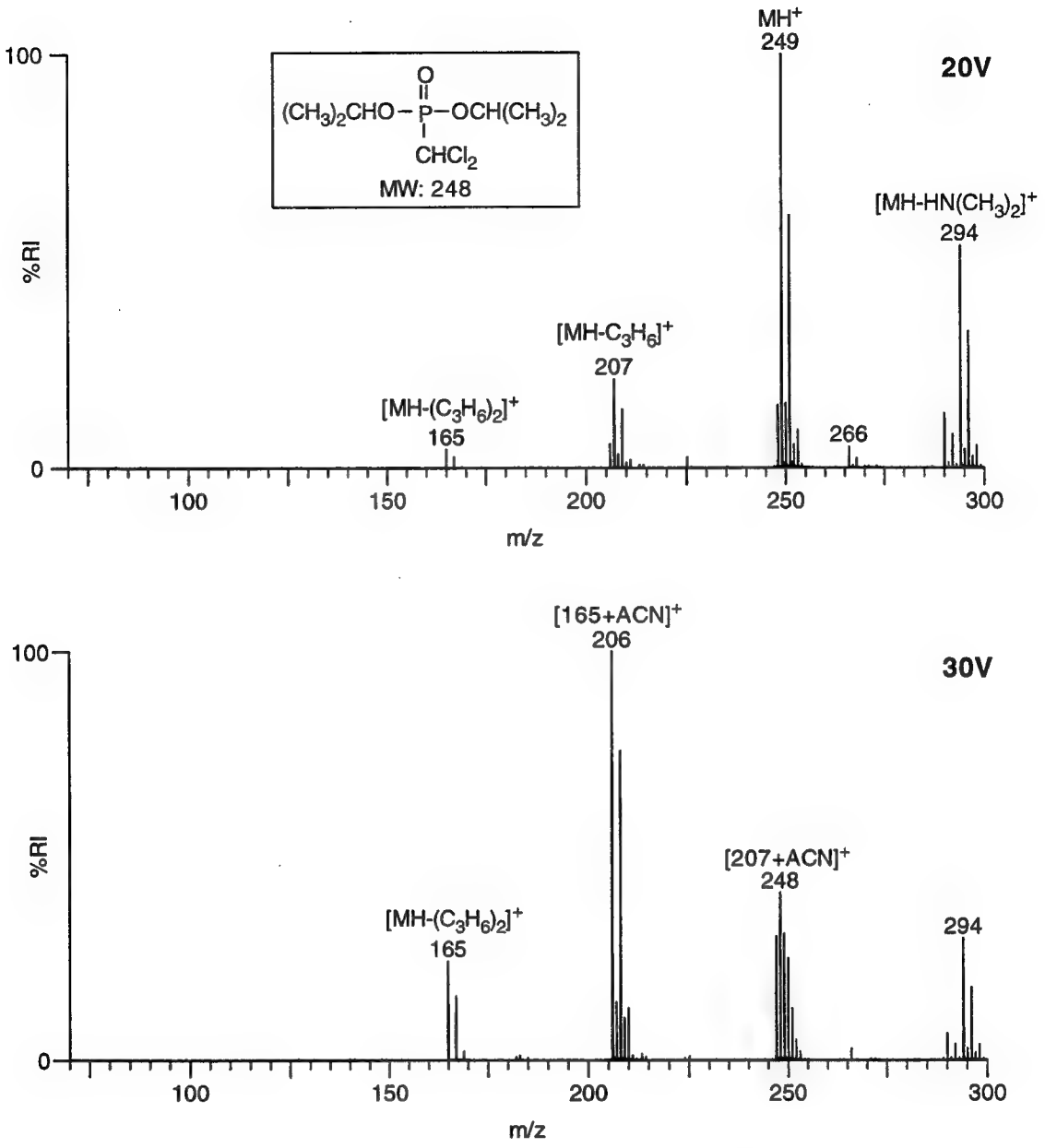


Figure 42. Diisopropyl dichloromethylphosphonate (248)

CAS: *55696-11-2*
Formula: *$C_7H_{15}Cl_2O_3P$*
Monoisotopic MW: *248.0136*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

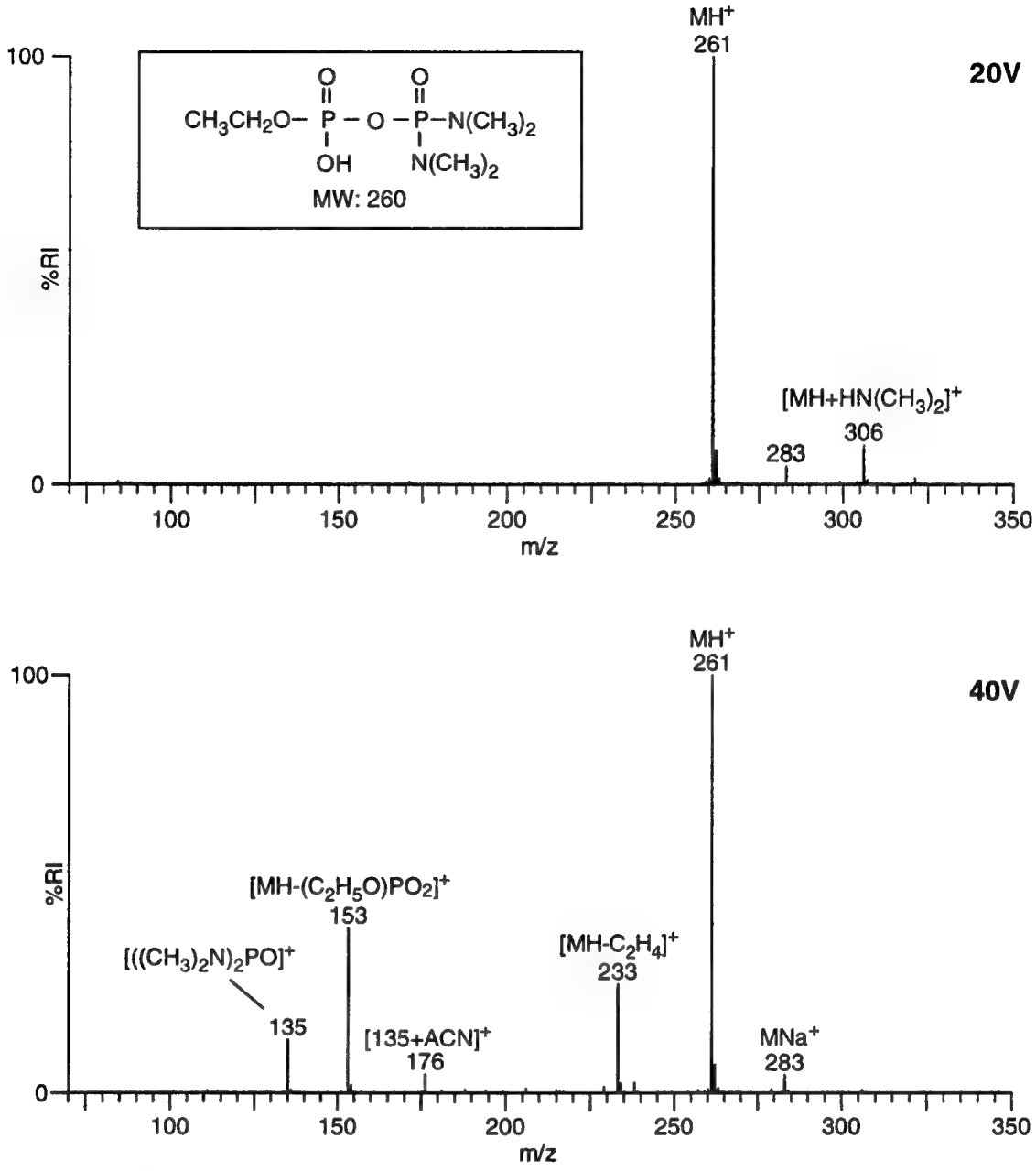


Figure 43. Ethyl phosphoric tetramethylphosphorodiamidic anhydride (260)

CAS:
Formula: $C_6H_{18}N_2O_5P_2$
Monoisotopic MW: *260.0691*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

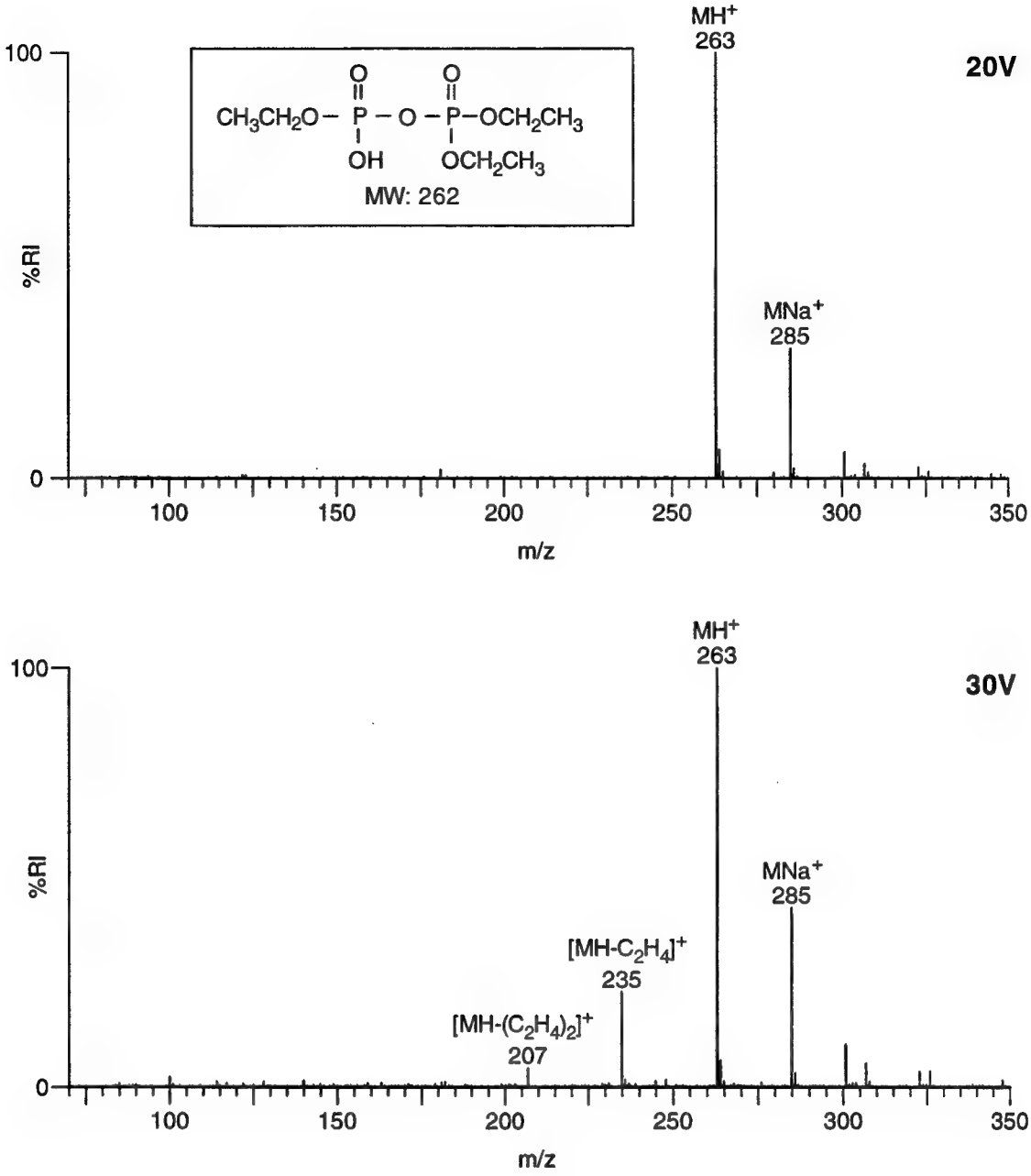


Figure 44. Diethyl phosphoric ethyl hydrogen phosphoric anhydride (262)

CAS: *20680-55-1*
Formula: *$C_6H_{16}O_7P_2$*
Monoisotopic MW: *262.0371*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

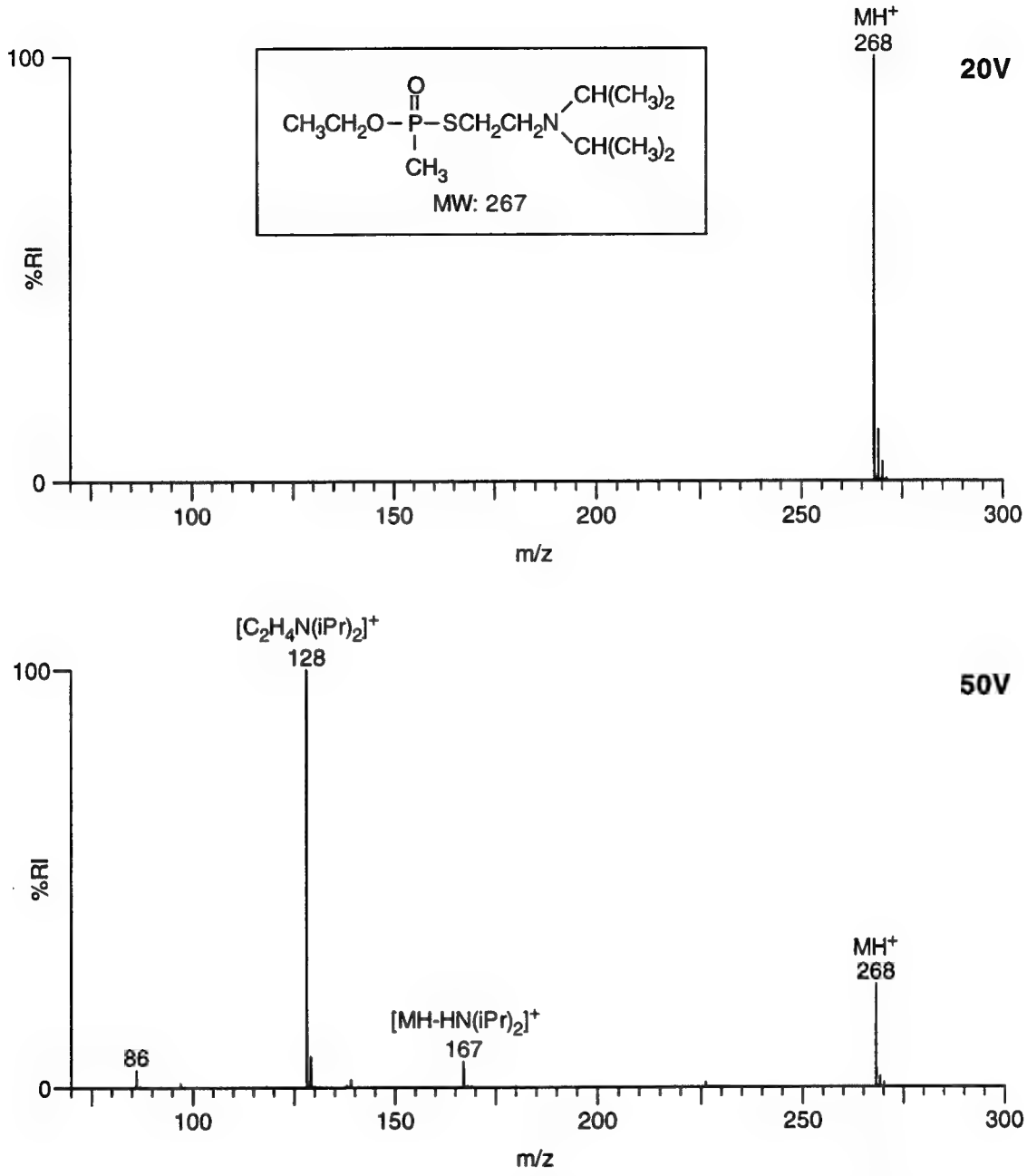


Figure 45. O-Ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothiolate (VX) (267)

CAS: *50782-69-9*
Formula: *$C_{11}H_{26}NO_2PS$*
Monoisotopic MW: *267.1422*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

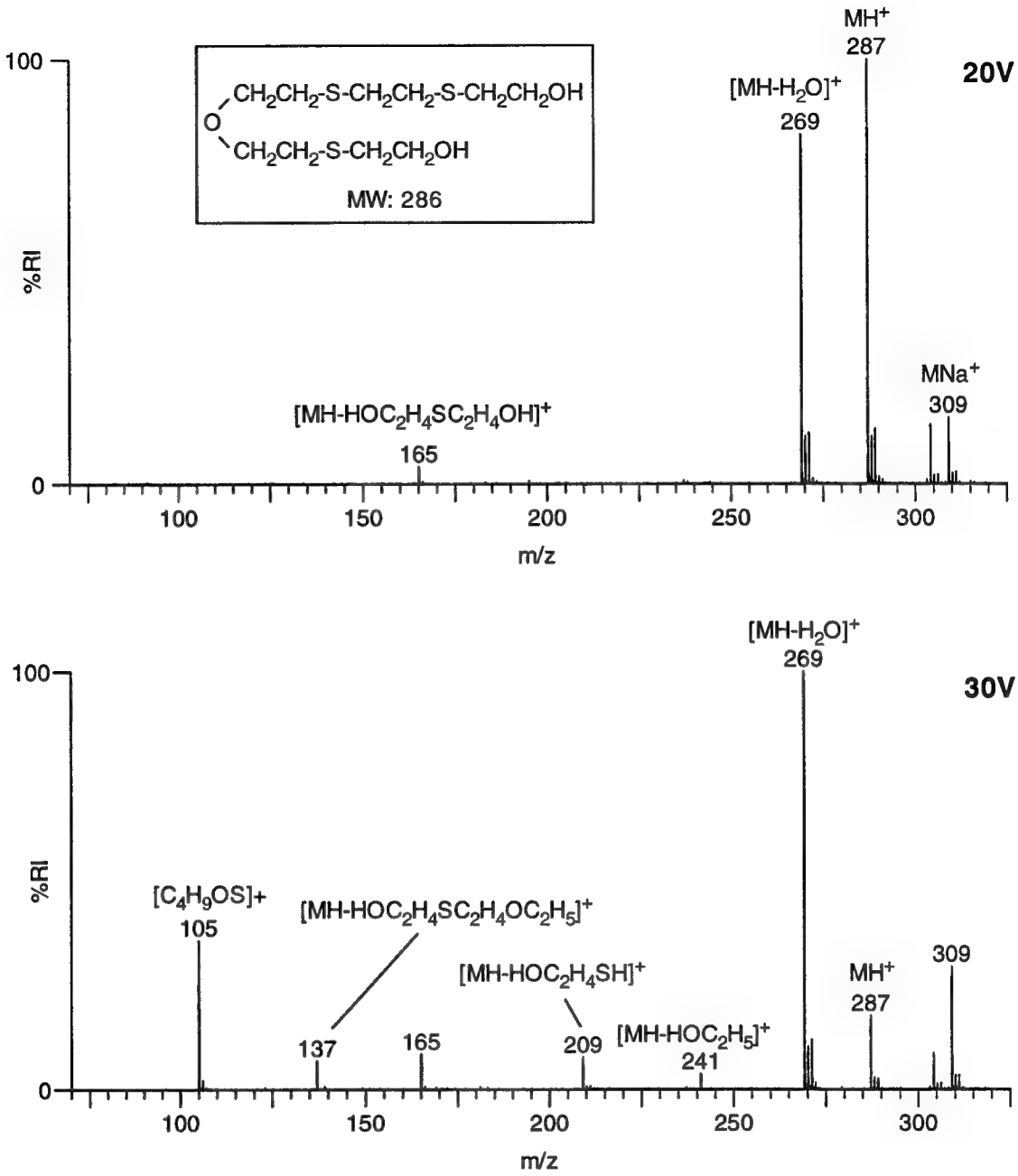


Figure 46. 6-Oxa-3,9,12-trithia-1,4-tetradecanediol (286)

CAS: *Unknown*
Formula: *$C_{10}H_{22}O_3S_3$*
Monoisotopic MW: *286.0731*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

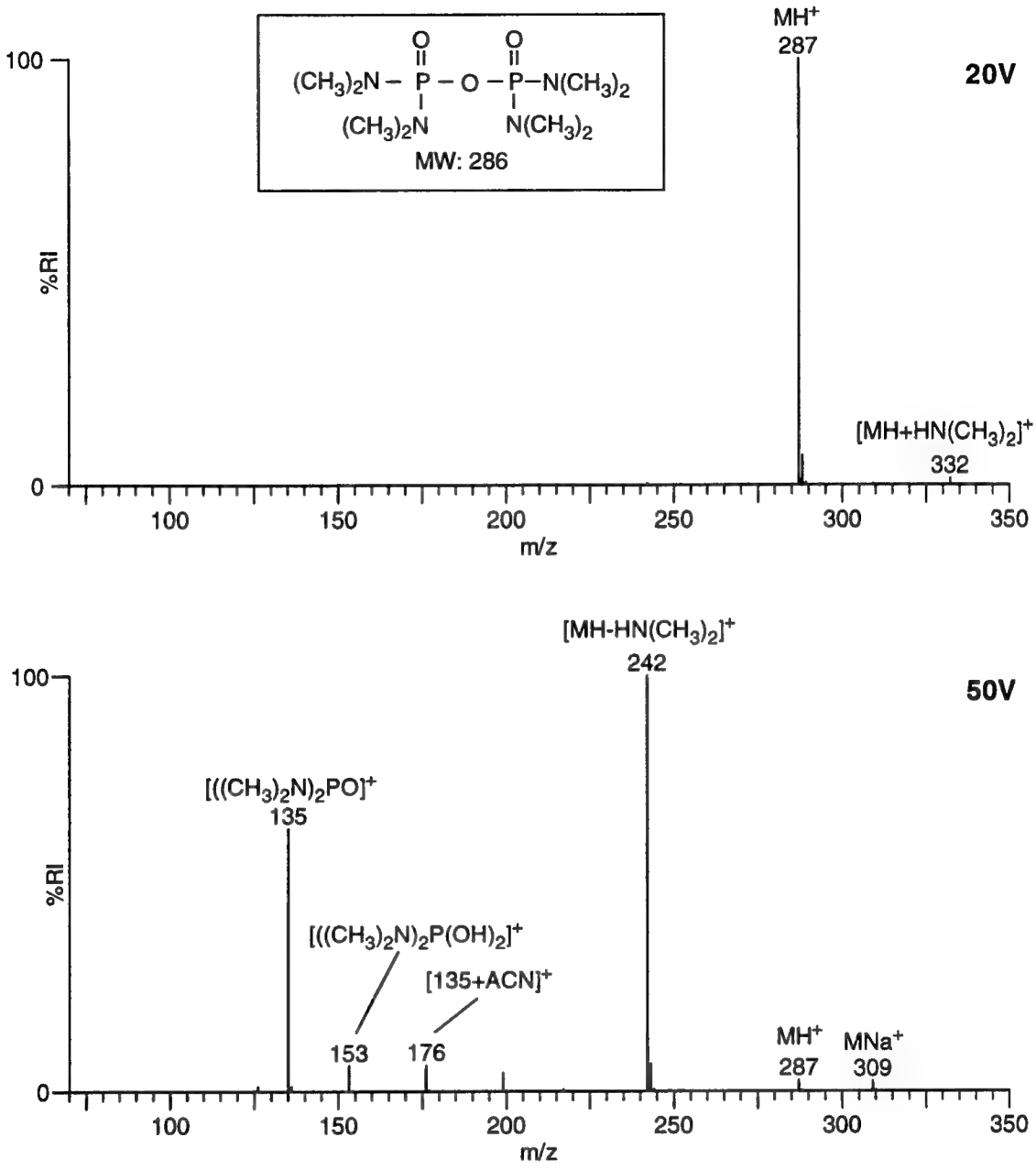


Figure 47. Bis(tetramethylphosphorodiamidic) anhydride (286)

CAS: *152-16-9*
Formula: *$C_8H_{24}N_4O_3P_2$*
Monoisotopic MW: *286.1324*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

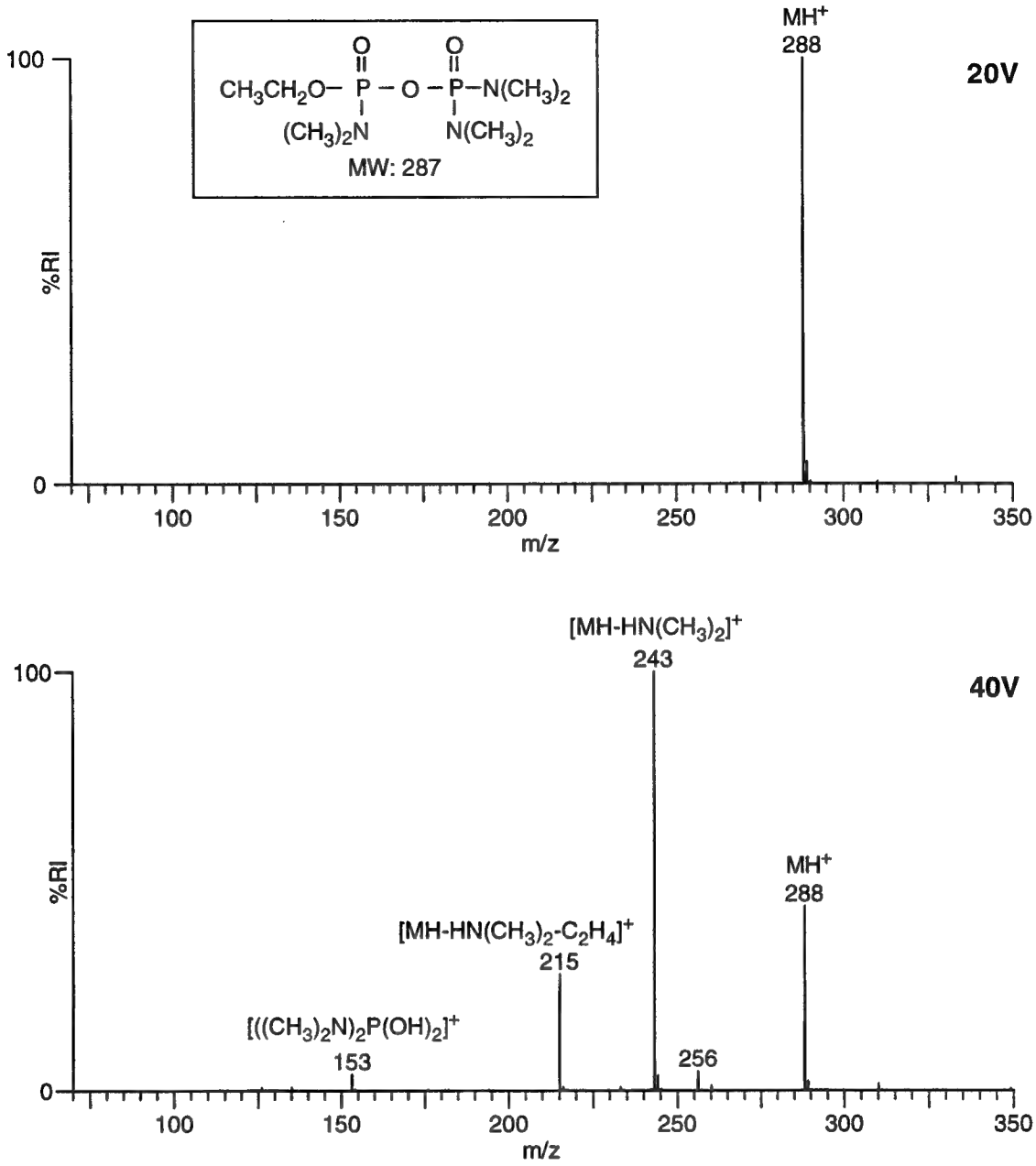


Figure 48. Ethyl dimethylphosphoramidic tetramethylphosphoamidic anhydride (287)

CAS: *29506-48-7*
Formula: *$C_8H_{23}N_3O_4P_2$*
Monoisotopic MW: *287.1164*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

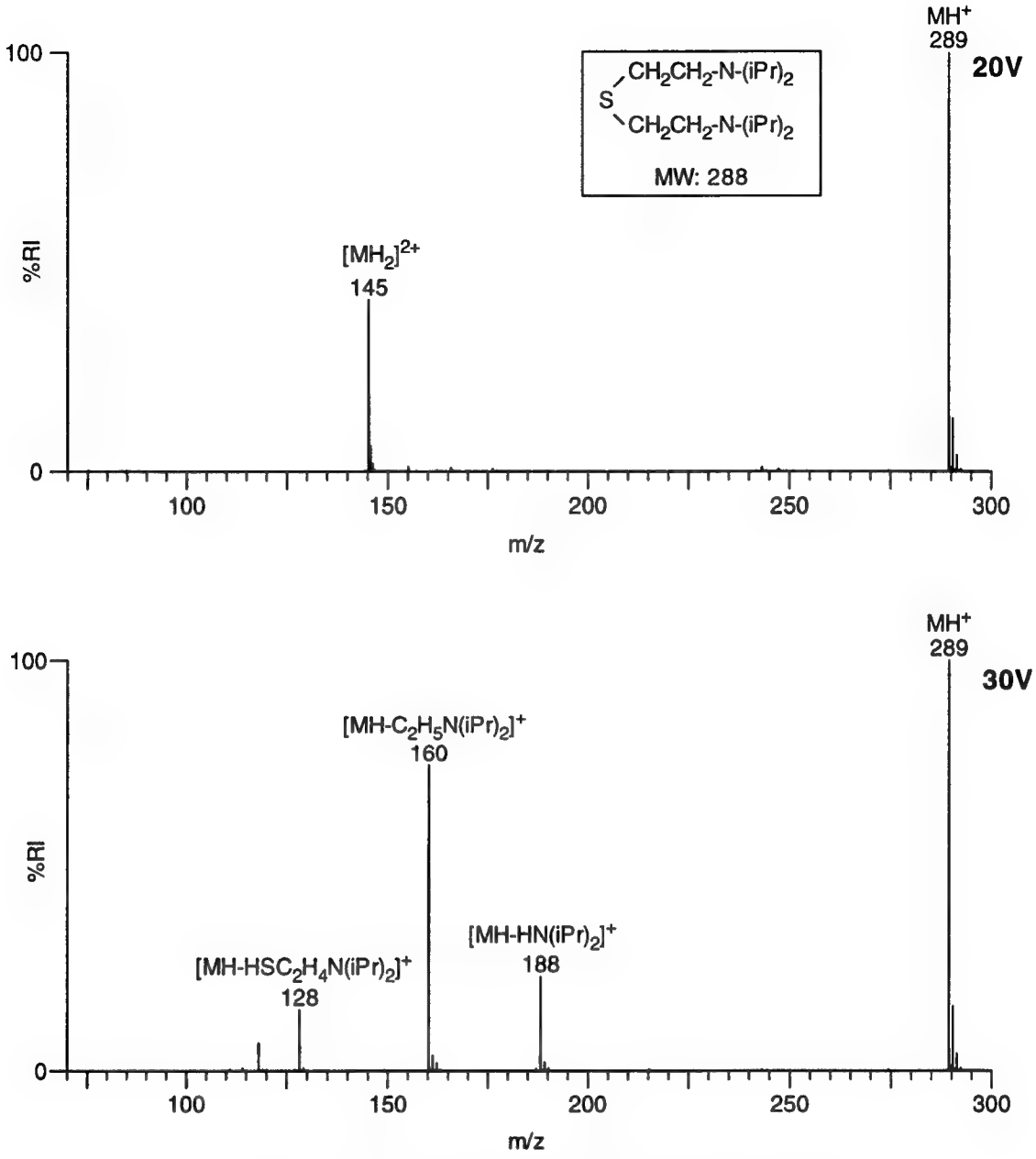


Figure 49. Bis[2-(diisopropylamino)ethyl] sulfide (288)

CAS: *110501-56-9*
Formula: *$C_{16}H_{36}N_2S$*
Monoisotopic MW: *288.2599*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

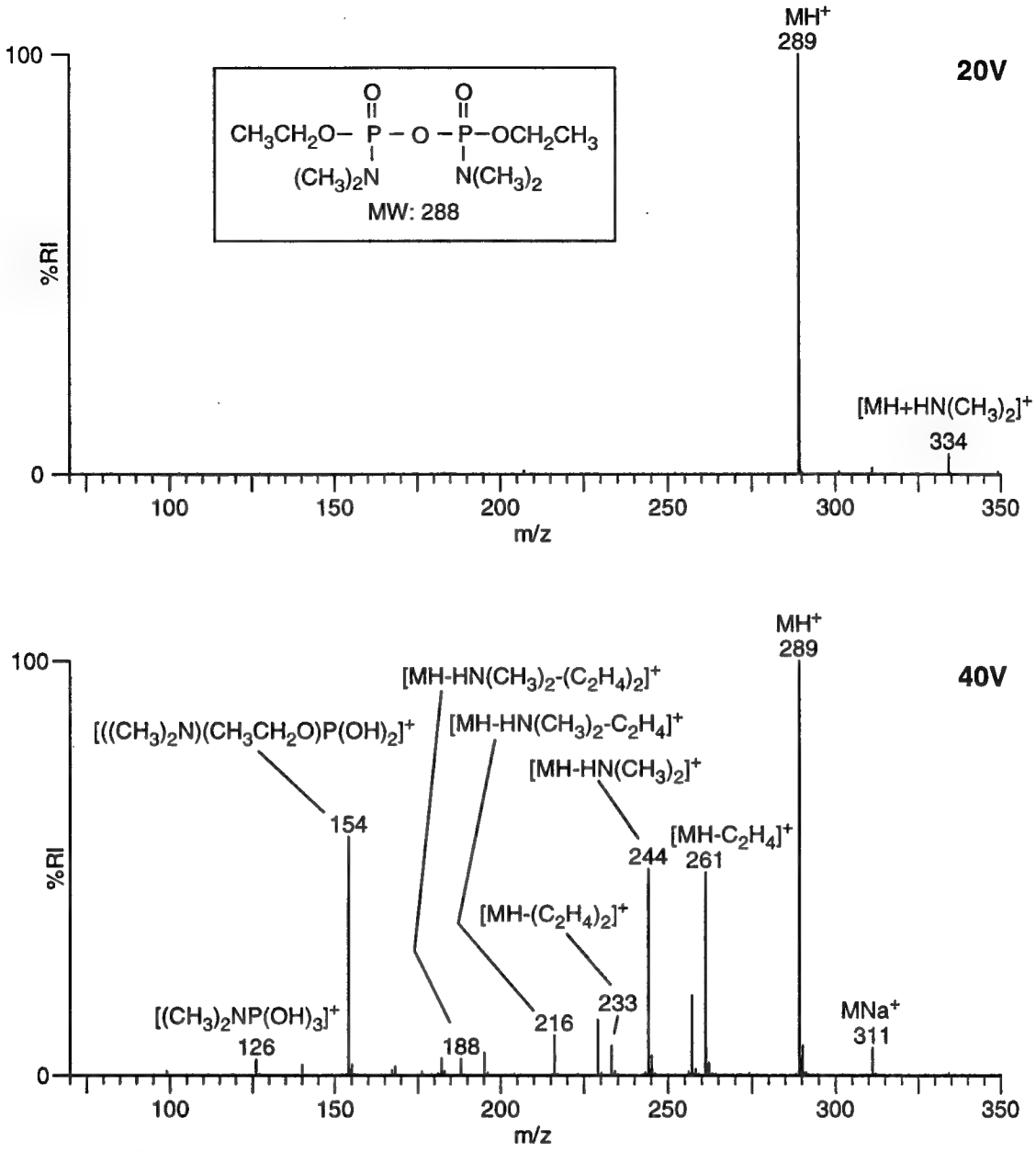


Figure 50. Bis(ethyl dimethylphosphoramidic) anhydride (288)

CAS: *28616-48-0*
Formula: *$C_8H_{22}N_2O_5P_2$*
Monoisotopic MW: *288.1004*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

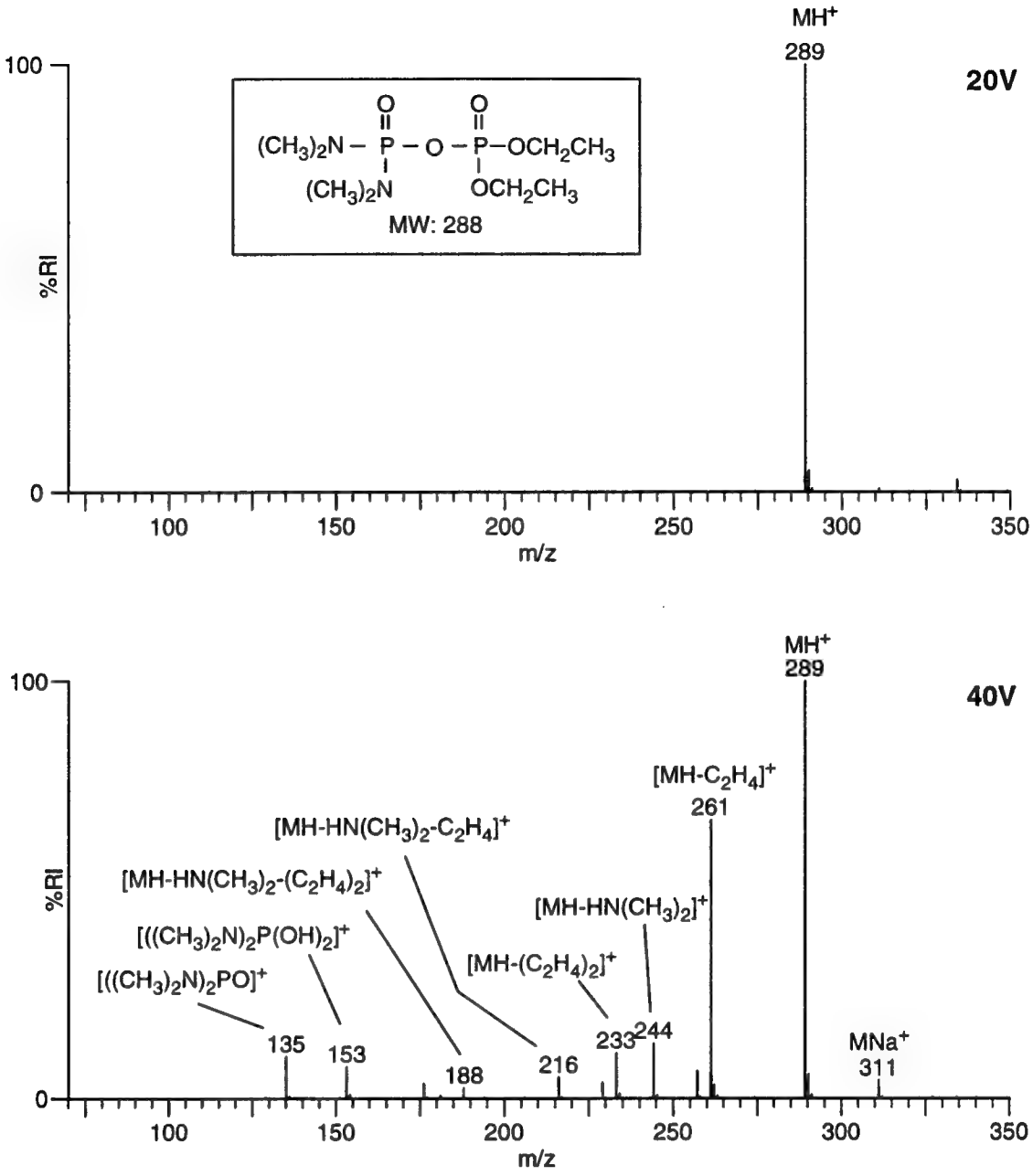


Figure 51. Diethyl phosphoric tetramethylphosphorodiamidic anhydride(288)

CAS: *1474-80-2*
Formula: *$C_8H_{22}N_2O_5P_2$*
Monoisotopic MW: *288.1004*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

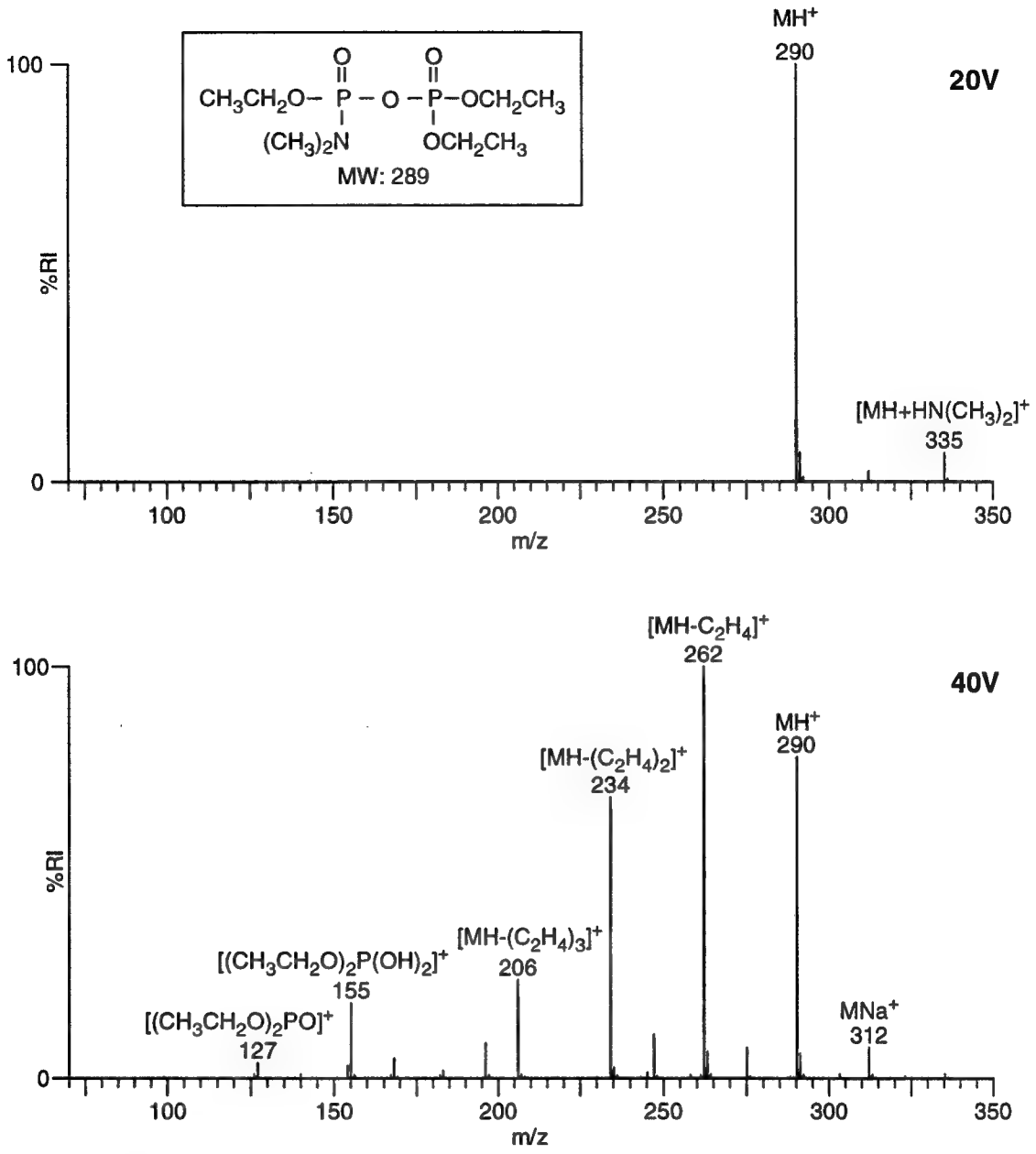


Figure 52. Diethyl phosphoric ethyl dimethylphosphoramidic anhydride (289)

CAS: *92403-54-8*
Formula: *$C_8H_{21}NO_6P_2$*
Monoisotopic MW: *289.0844*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

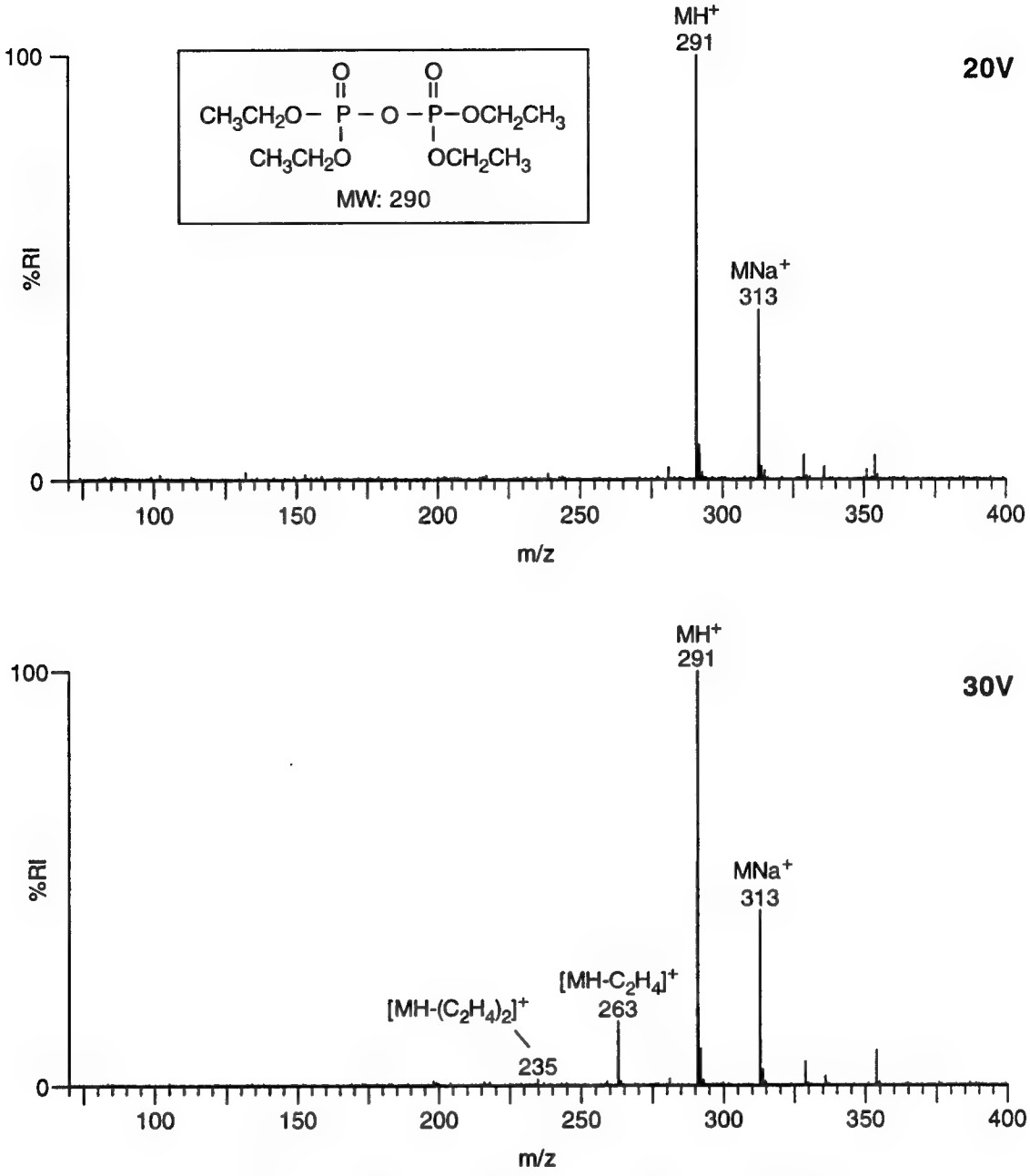


Figure 53. Bis(diethyl phosphoric) anhydride (TEPP) (290)

CAS: *107-49-3*
Formula: *$C_8H_{20}O_7P_2$*
Monoisotopic MW: *290.0684*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

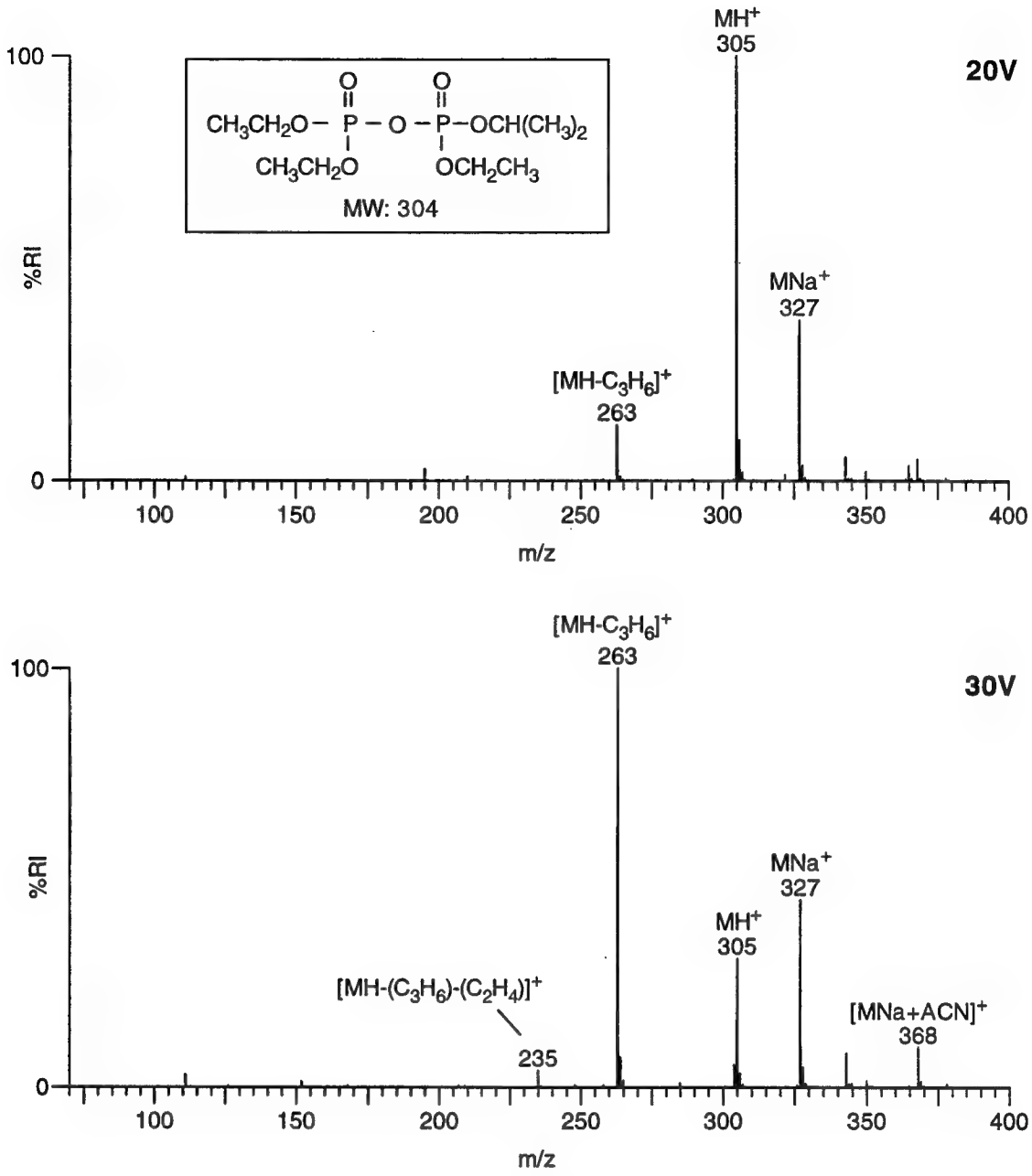


Figure 54. Diethyl phosphoric ethyl isopropyl phosphoric anhydride (304)

CAS: *120551-44-2*
Formula: *$C_9H_{22}O_7P_2$*
Monoisotopic MW: *304.0841*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

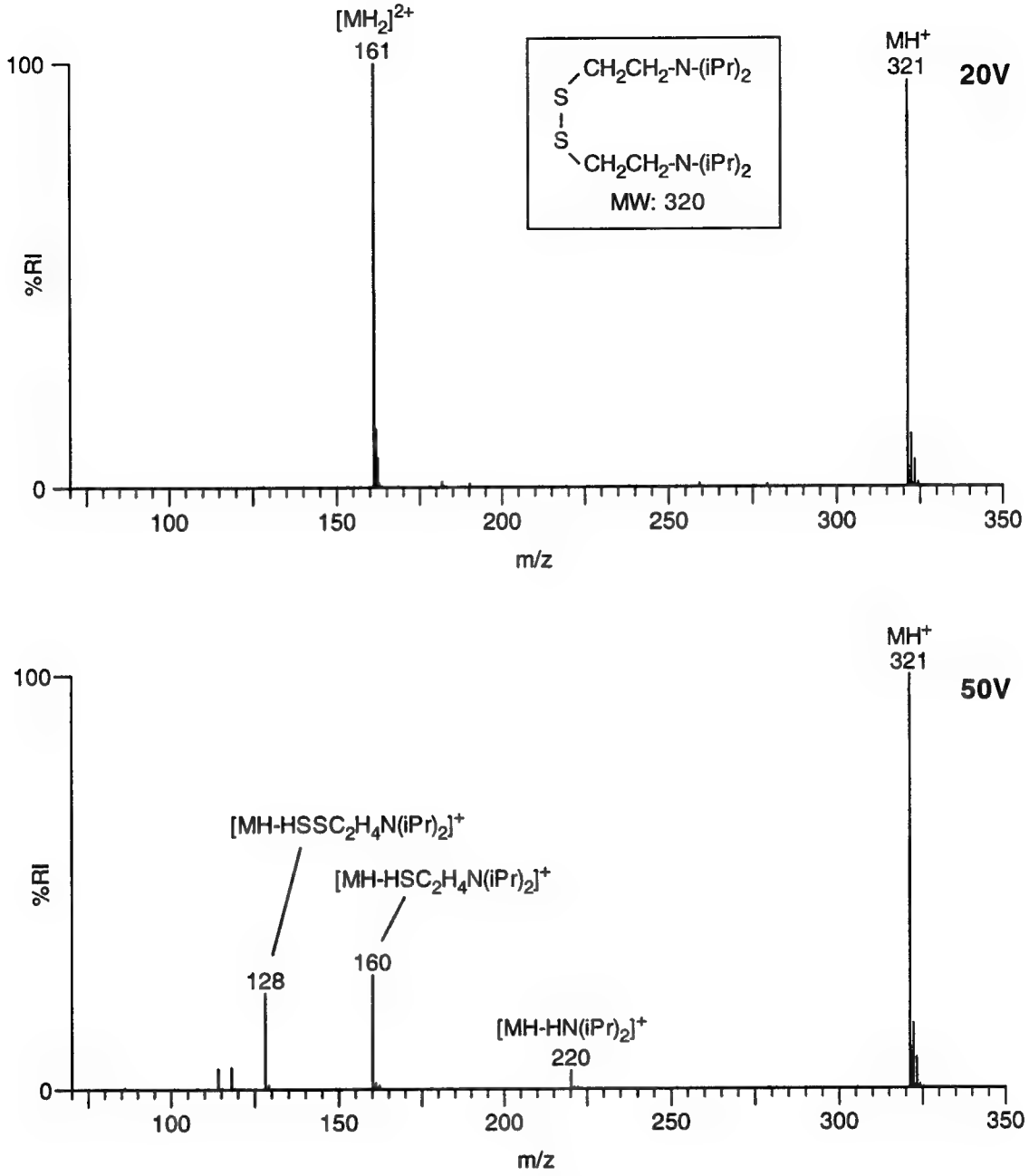


Figure 55. Bis[2-diisopropylamino)ethyl] disulfide (320)

CAS: *65332-44-7*
Formula: *$C_{16}H_{36}N_2S_2$*
Monoisotopic MW: *320.2320*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

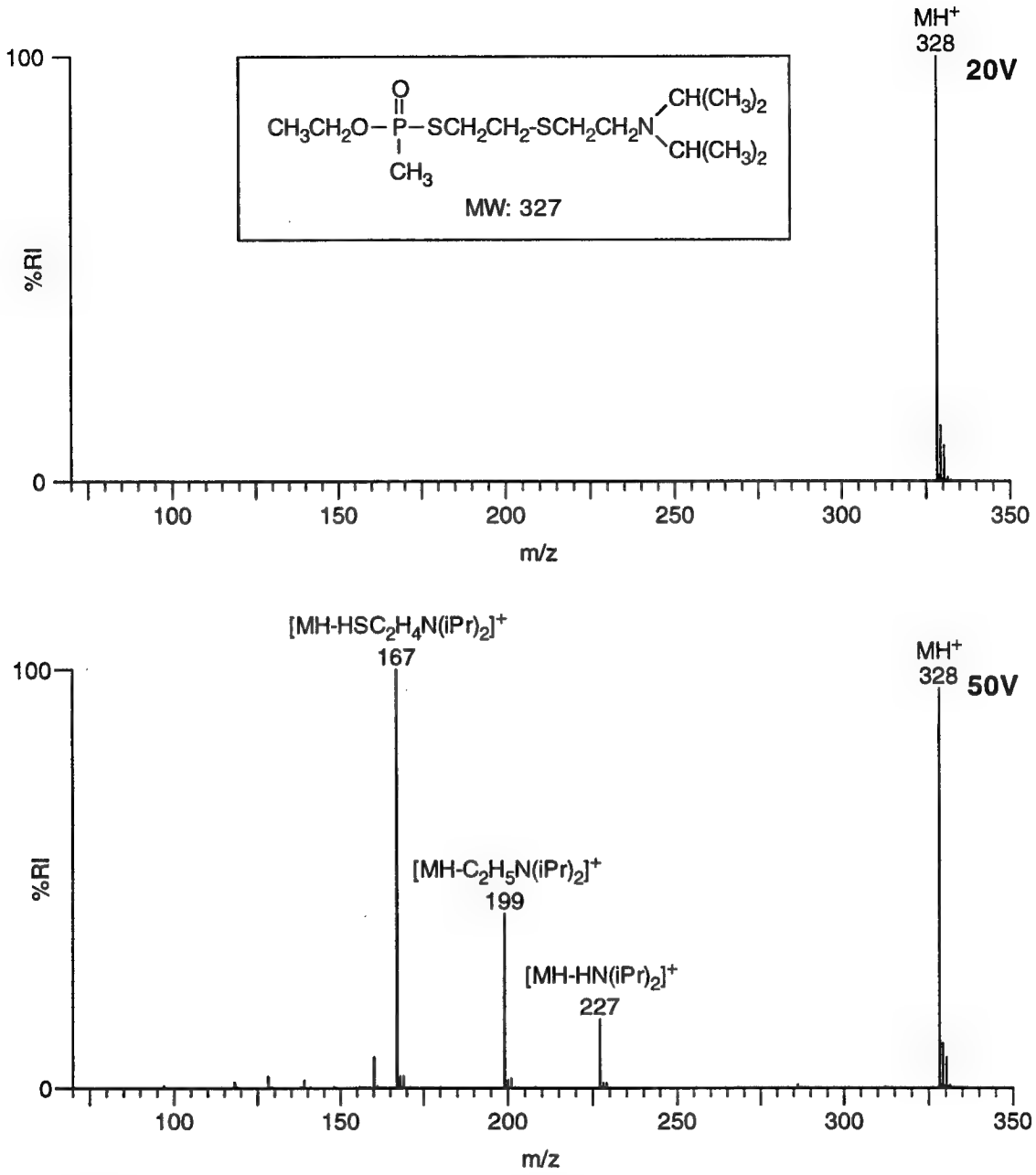


Figure 56. O-Ethyl-S-[5-(diisopropylamino)-3-thiapentyl] methylphosphonothiolate (327)

CAS: *110501-57-0*
Formula: *$C_{13}H_{30}NO_2PS_2$*
Monoisotopic MW: *327.1456*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

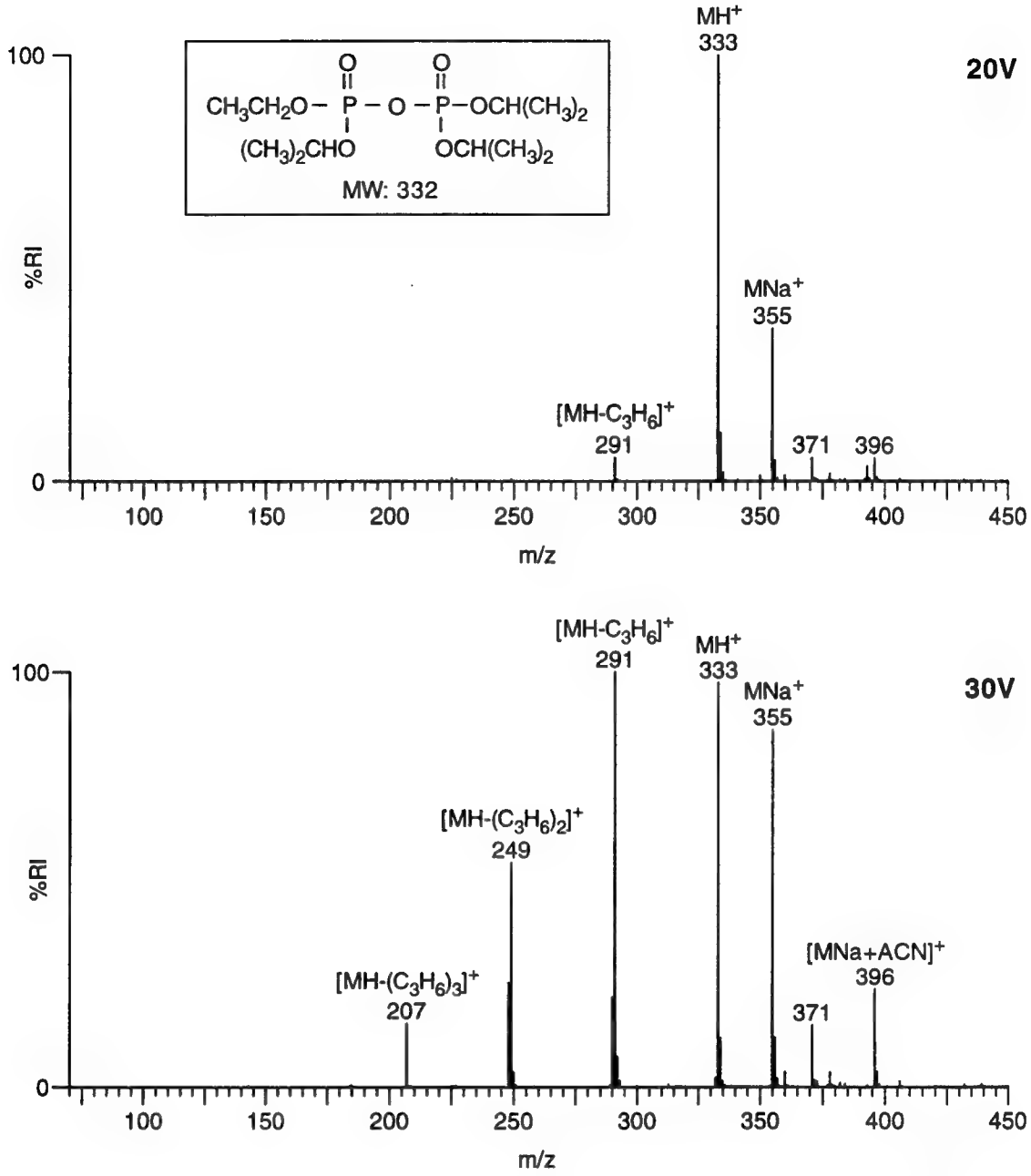


Figure 57. Diisopropyl phosphoric ethyl isopropyl phosphoric anhydride (332)

CAS: *63704-58-5*
Formula: *$C_{11}H_{26}O_7P_2$*
Monoisotopic MW: *332.1154*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

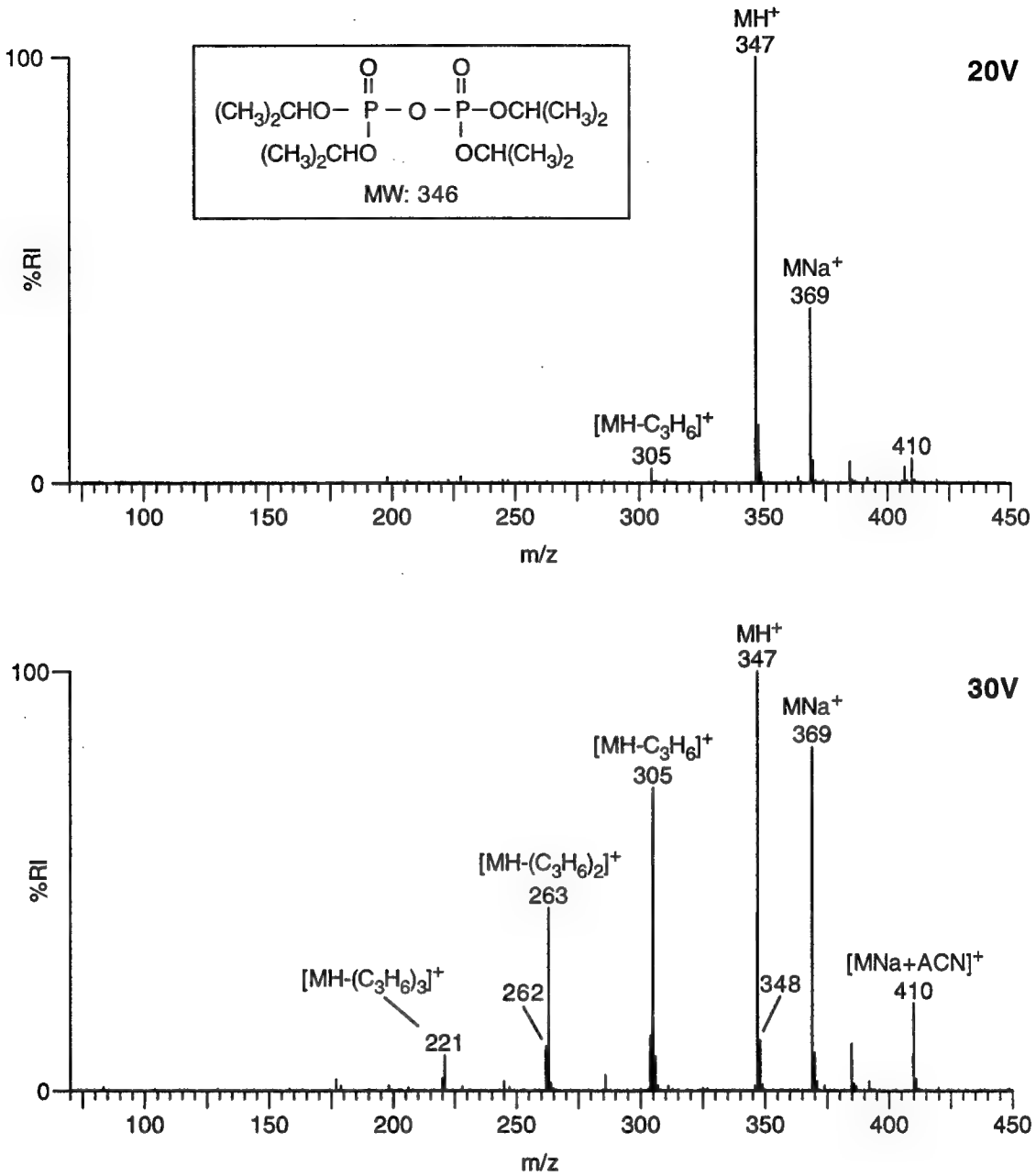


Figure 58. Bis(diisopropylphosphoric) anhydride (346)

CAS: *5836-28-2*
Formula: *$C_{12}H_{28}O_7P_2$*
Monoisotopic MW: *346.1310*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

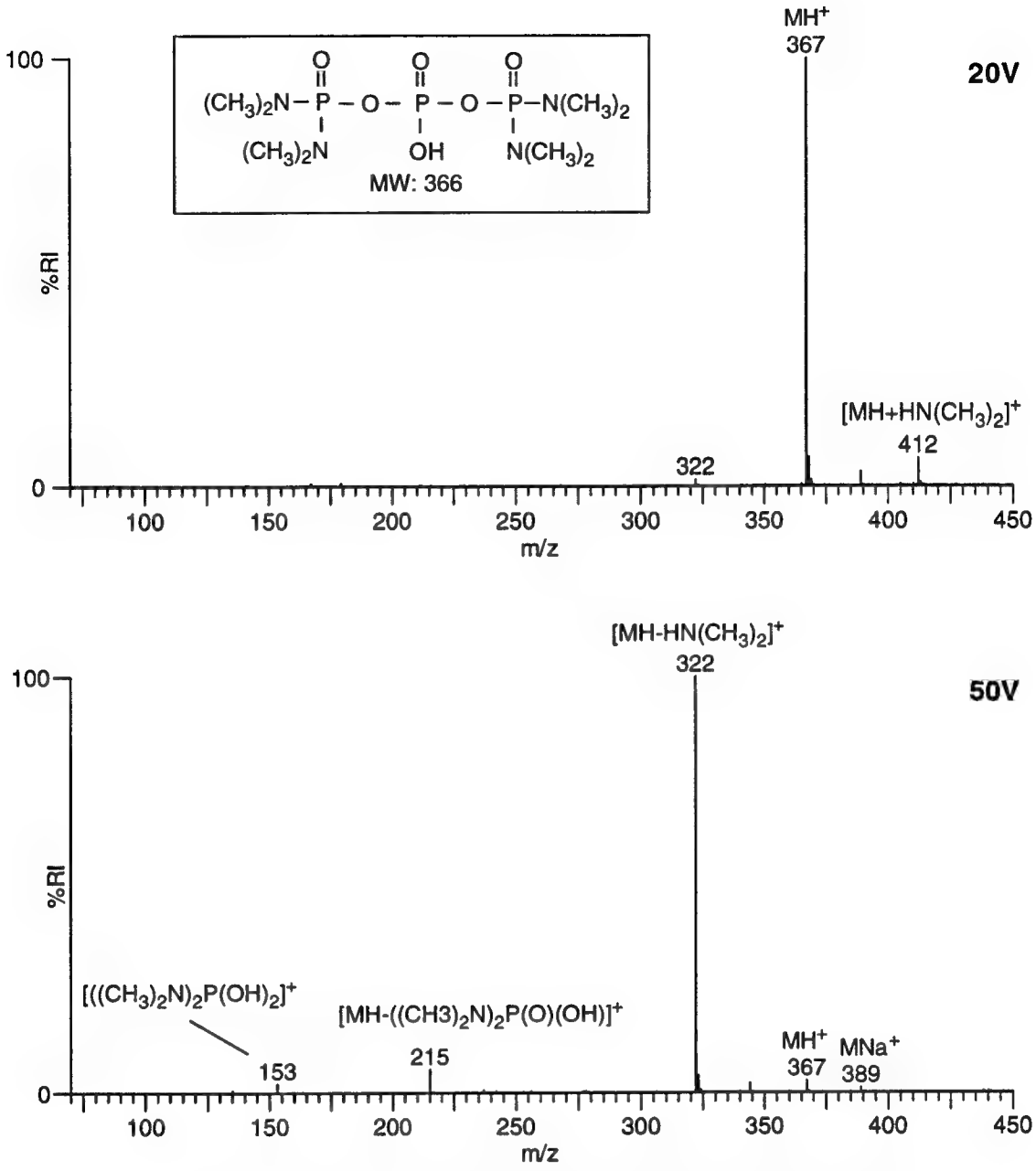


Figure 59. Octamethyltetramidotriphosphoric acid (or isomer) (366)

CAS:
Formula: $C_8H_{25}N_4O_6P_3$
Monoisotopic MW: *366.0987*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

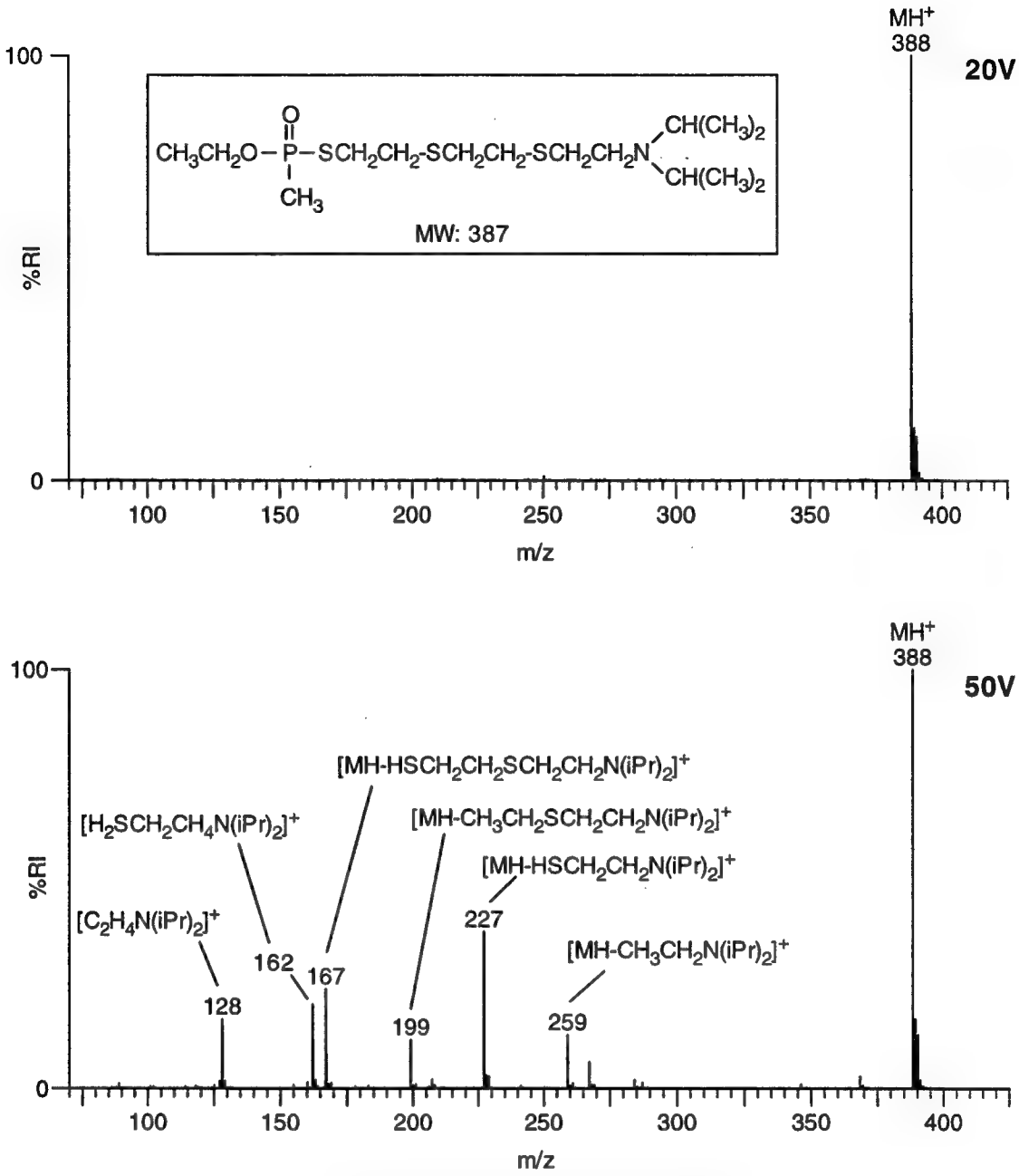


Figure 60. O-Ethyl-S[8-(diisopropylamino)-3,6-dithiaoctyl] methylphosphonothiolate (387)

CAS: *110501-60-5*
Formula: *$C_{15}H_{34}NO_2PS_3$*
Monoisotopic MW: *387.1489*
Instrumental: *LC-ESI-MS (ACN/H_2O) using a Micromass LCT™*

Conclusions

LC-ESI-MS provides an advantage over GC-MS for the analysis of aqueous samples and extracts, as both the chemical warfare agents and their hydrolysis products may be analysed at the nanogram to picogram level during a single analysis without the need for additional sample handling or derivatization. Over the past several years DRES developed LC-ESI-MS methods for the analysis of a variety of contaminated samples including; hydrolysed munitions grade mustard, degraded O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothiolate (VX), snow contaminated with sarin (GB), soil contaminated with sarin (GB) and soman (GD), munitions grade tabun (GA), failed synthetic products and synthetic standards. During the course of these investigations DRES acquired ESI-MS data for sixty chemical warfare agents, degradation products and related compounds. Data were obtained with a resolution of 5000 (50% valley definition) in the continuum mode at several sampling cone voltages. At lower sampling cone voltages the mass spectra were dominated by protonated, sodiated and protonated acetonitrile adducts and/or their dimers that could be used to confirm the molecular mass of each compound. Structural information was obtained by inducing product ion formation in the ESI interface at higher sampling cone voltages.

Representative data obtained at both lower and higher sampling cone voltages were selected for entry into the DRES ESI-MS Database as part of a collaboration between Canada (DRES) and The Netherlands (TNO Prins Maurits Laboratory). The reported data should prove valuable for the identification of chemical warfare agents, degradation products and related compounds samples collected by the military or in support of Chemical Weapons Convention inspections.

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